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ANNALS of SURGERY

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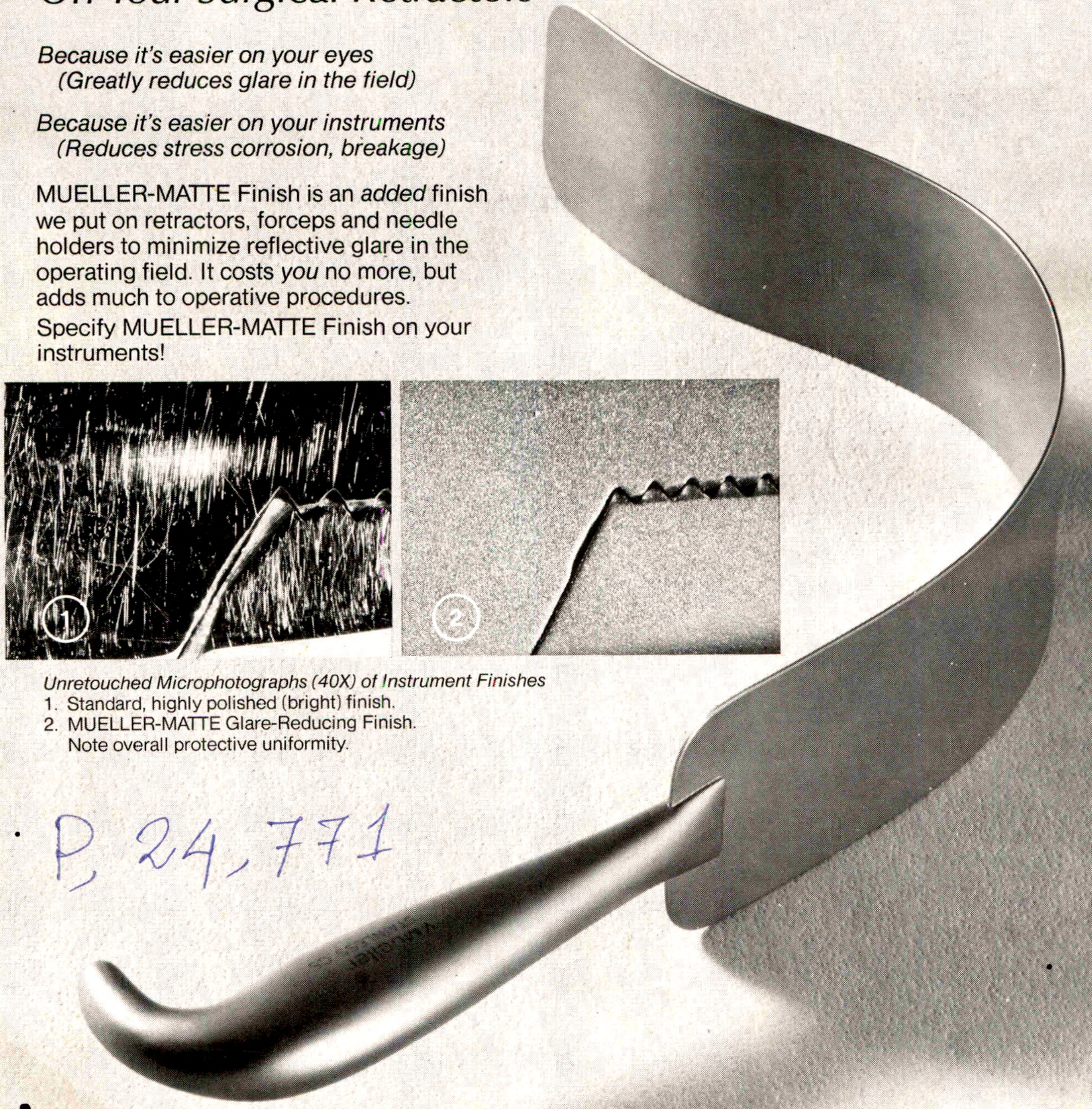

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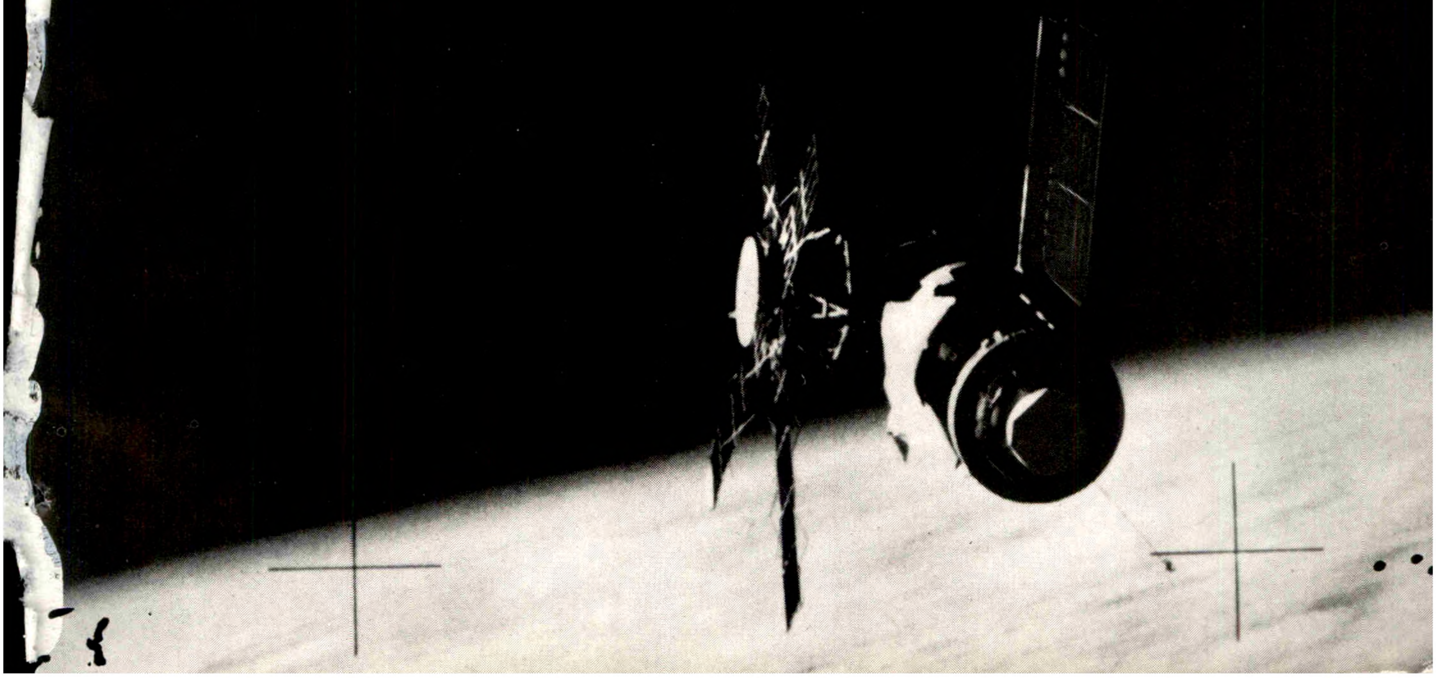

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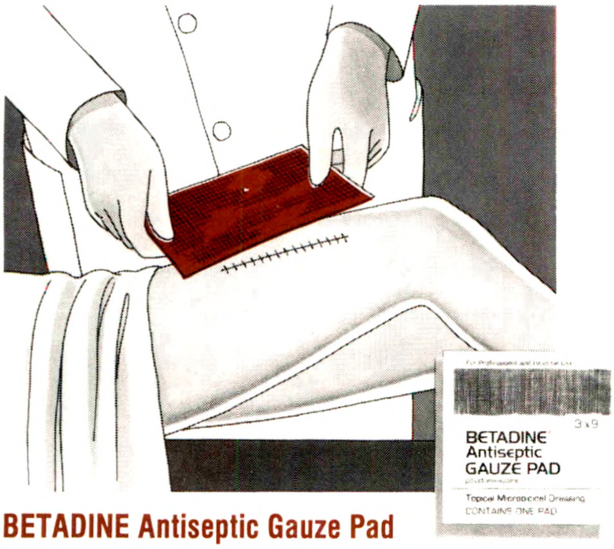

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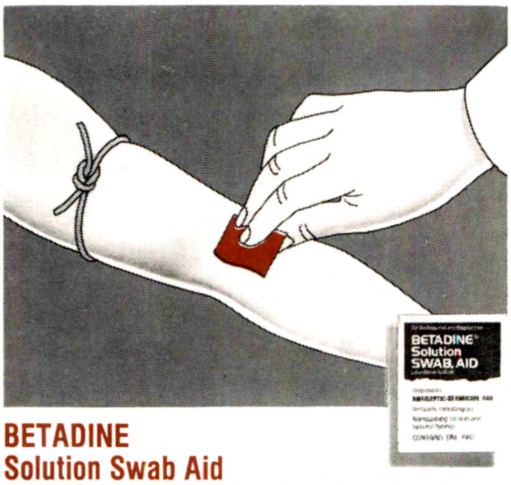

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ANNALS OF SURGERY

Vol. 183 January 1976 No. 1

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REFERENCES: 1. Webb, W. R., and Degerli, I. U.: Acetylcysteine as a mucolytic agent in clinical practice, Clin. Med. *71*:1531-1539 (Sept.) 1964. **2.** Thomas, P. A., Lynch, R. E., and Merrigan, E. H.: Prevention of postoperative pulmonary atelectasis: Review of 215 cases and evaluation of acetylcysteine, Am. Surg. *32*:301-307 (May) 1966. **3.** Webb, W. R.: New mucolytic agents for sputum liquefaction, Postgrad. Med. *36*:449-453 (Nov.) 1964. **4.** Tarnay, T. J., Wittig, H. J., Lucas, R. V., Jr., and Warden, H. E.: Chronic and recurrent atelectasis in children, Surgery *62*:520-529 (Sept.) 1967.

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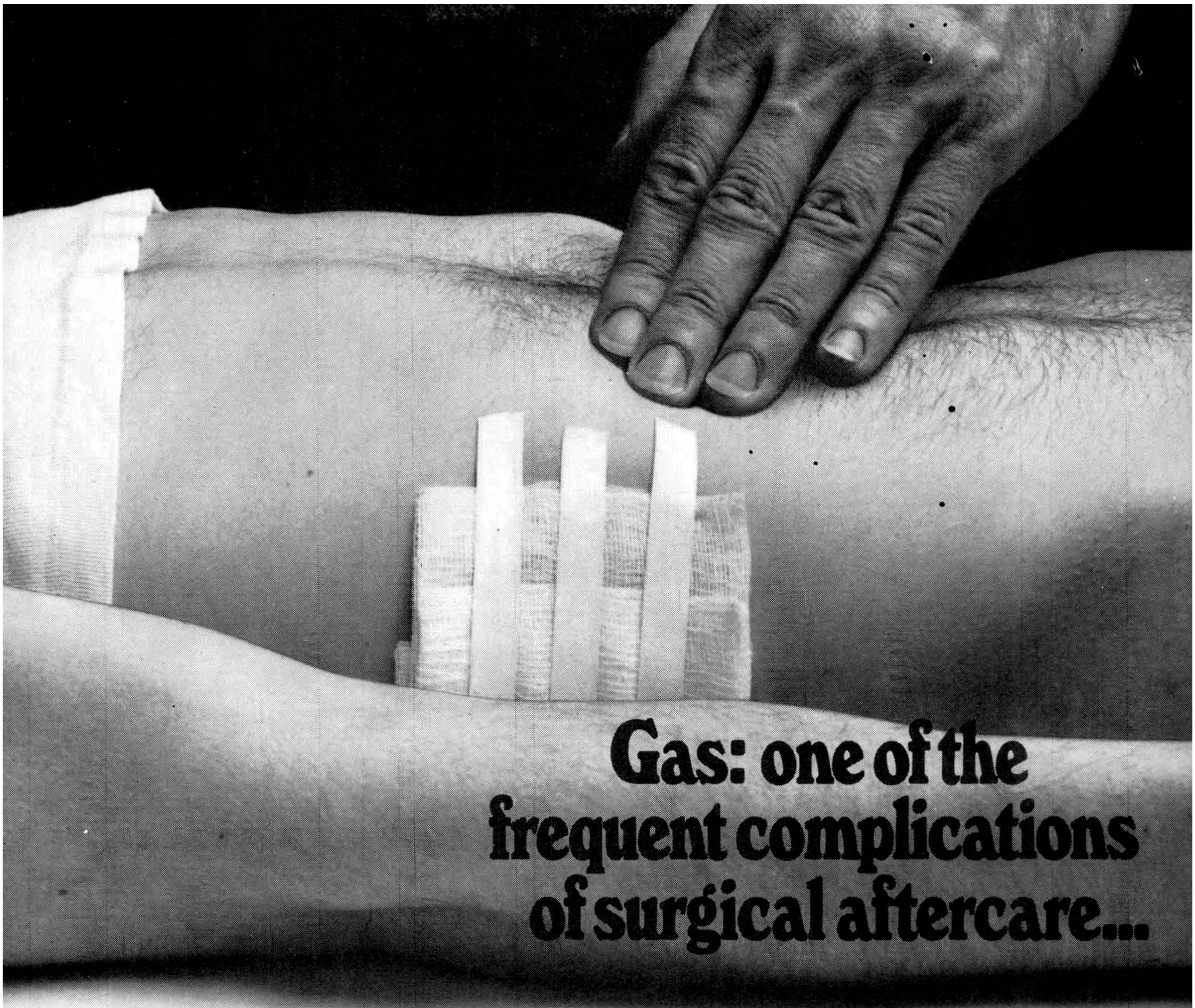
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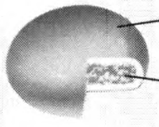

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1. Gibstein, A., *et al.*: Prevention of postoperative abdominal distention and discomfort with simethicone, *Obstet. Gynecol. 38*:386, Sept. 1971.
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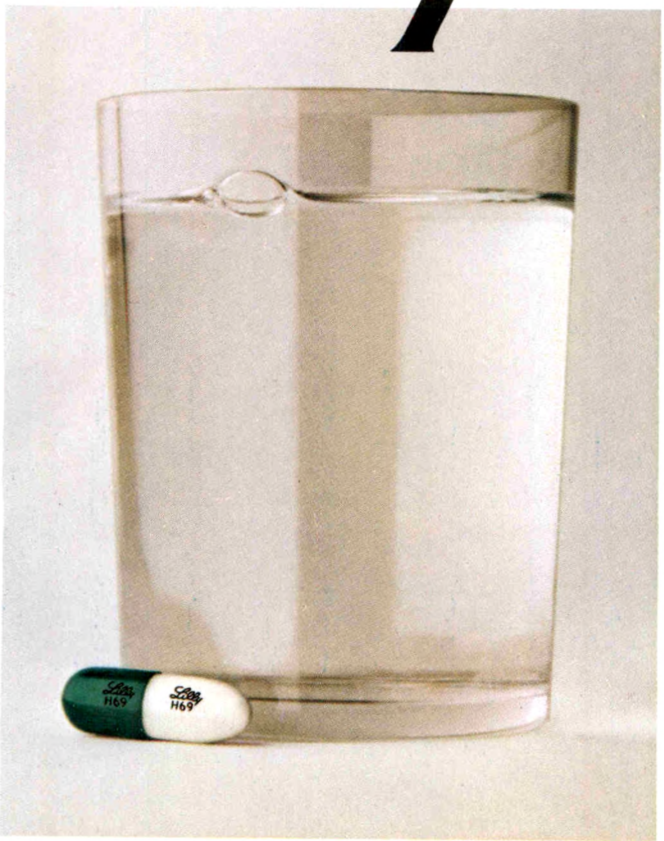

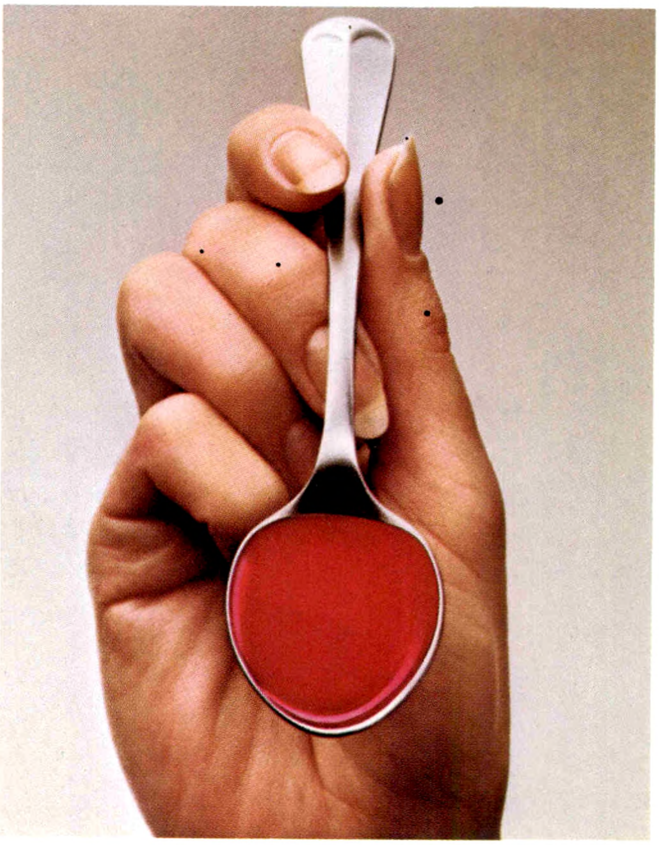

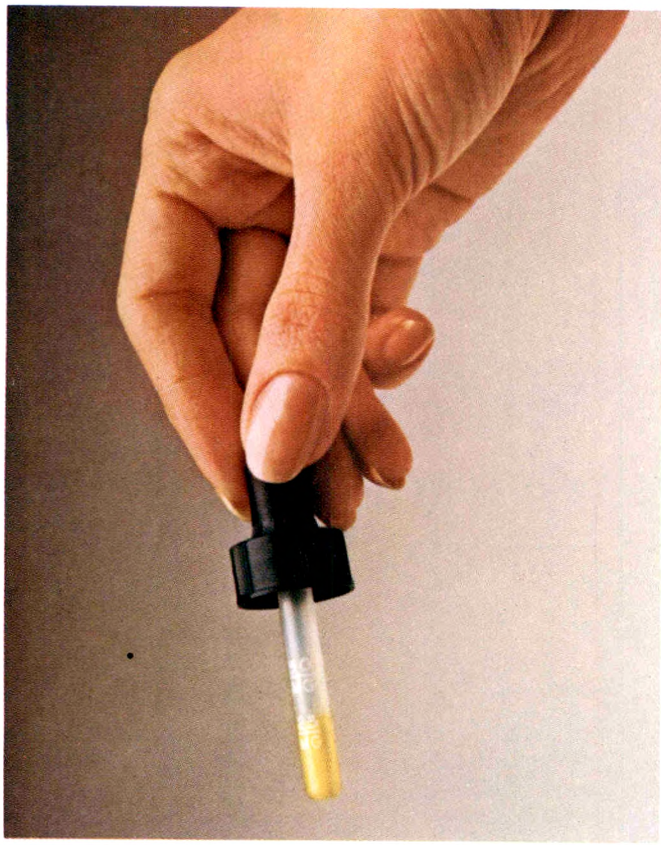

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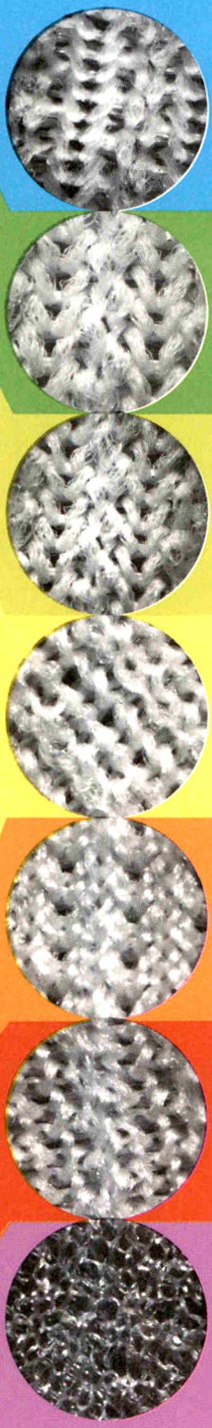

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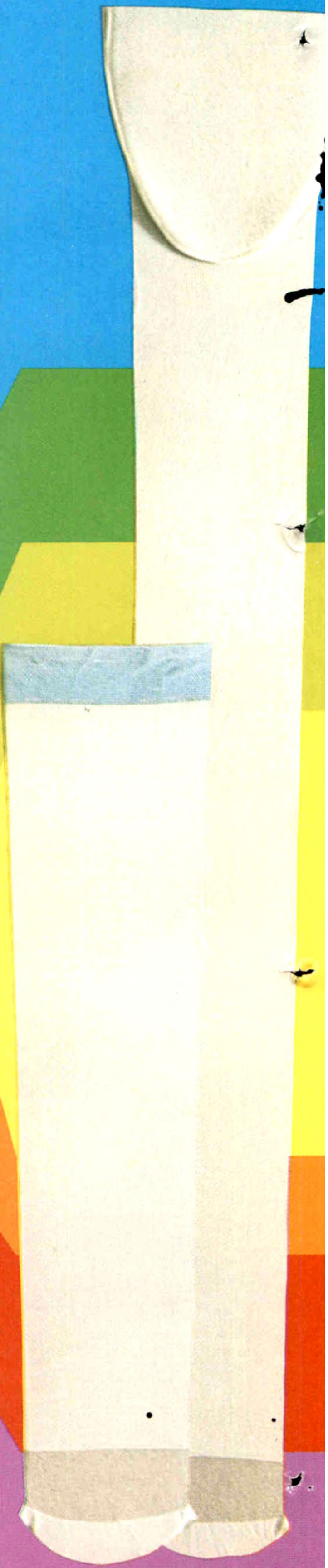

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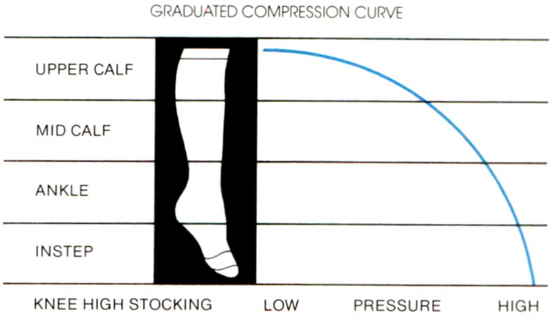

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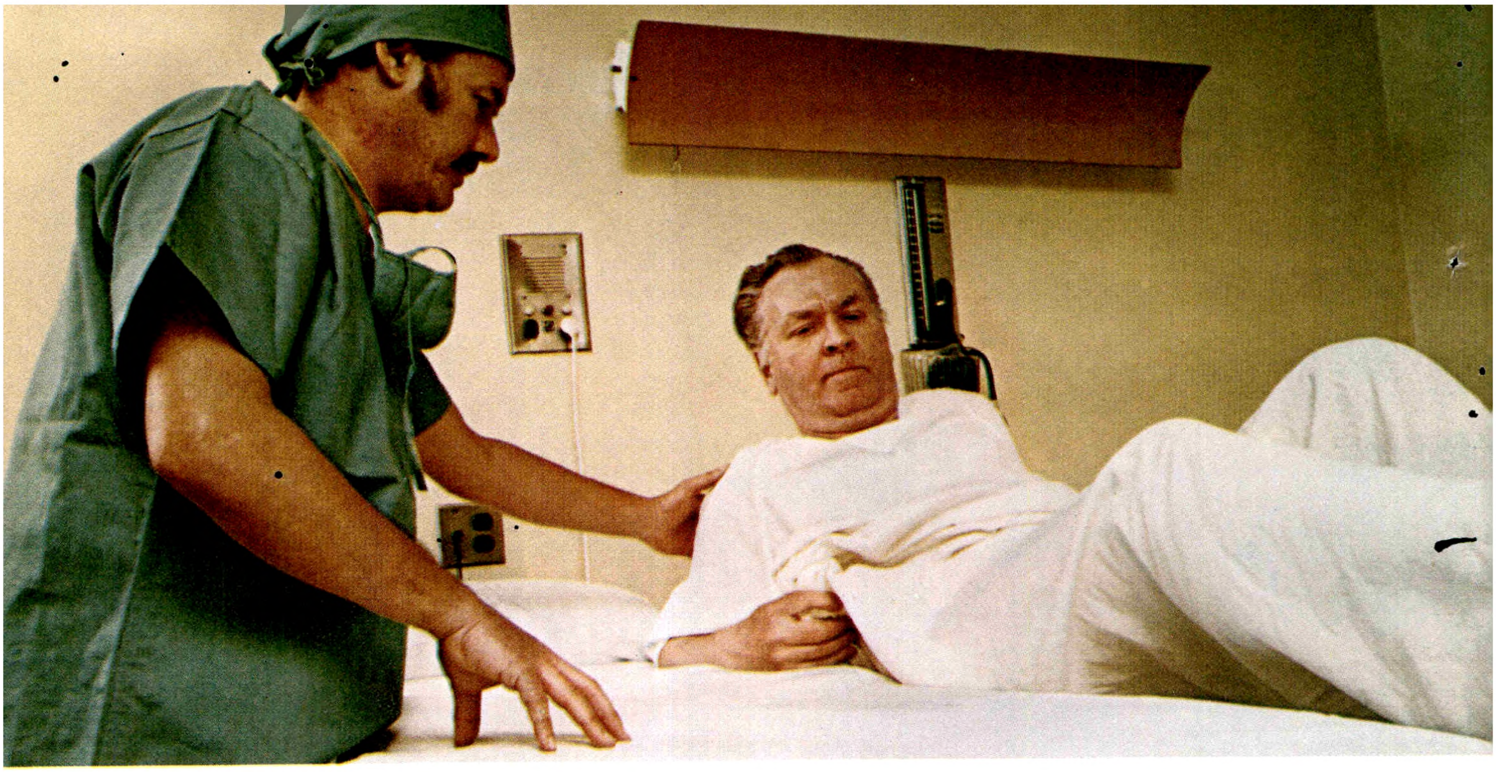

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5mg/ml

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Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus and severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic and surgical procedures; cardioversion.

Contraindicated: In infants; in patients with known hypersensitivity to the drug; in acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *When used I.V., the following procedures should be undertaken to reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment. Inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; extreme care should be taken to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Administer with extreme care to elderly or very ill and those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; have resuscitative facilities available. When used with narcotic analgesic eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, nursing women or women of childbearing potential, weigh expected benefit against possible hazard to mother and child. Not recommended for OB use.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm and increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic and have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly and debilitated; safety and efficacy in children under 12 not established.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis and phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial adult dose is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., *dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Moderate psychoneurotic reactions, 2 to 5 mg I.M. or I.V. and severe psychoneurotic reactions, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary; muscle spasm, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); status epilepticus, severe recurrent convulsive seizures, 5 to 10 mg I.M. or I.V. initially, repeat in 2 to 4 hours if necessary. In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V., within 5 to 10 min. prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma and diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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Extended Use of Intra-aortic Balloon Pumping in Peripartum Cardiomyopathy

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A patient with perinatal cardiomyopathy was greatly benefited physiologically by 7 weeks of intra-aortic balloon pumping. This experience documented that extended pumping can be carried out with only manageable complications. Although the patient survived the hospitalization, she died shortly thereafter of intractable congestive failure. Perinatal cardiomyopathy is a potentially reversible condition. Ventricular assistance by intra-aortic balloon pumping may be sustaining during continued systemic treatment of this entity. Further evaluation for longevity of more advanced congestive heart failure from cardiomyopathies needs further clinical trial.

WIDE EXPERIENCE reported by many authors has documented the usefulness of intra-aortic balloon pumping as an adjunct to the treatment of various forms of cardiogenic shock.[2,8,11,13] In spite of the now frequent use of this technique for short term assist of patients with myocardial infarction, the limitations of balloon pumping are still being defined. The length of time that balloon pumping can be safely used, the maximum pump run producing long term patient benefit, and the usefulness in more chronic forms of cardiogenic shock remain to be elucidated. The suggestion that recovery from perinatal cardiomyopathy may be expected if the patient survives the initial episode of heart failure prompted this attempt to assist a terminal patient with this disease. Experience in treating this patient provides important information about the limits of intra-aortic balloon pumping.

Case Report

M.M., a 43-year-old Caucasian primagravida, was transferred to St. Luke's Hospital on October 8, 1973. Although her life had been characterized by good health, her pregnancy had been complicated by congestive heart failure and pulmonary edema, and macrocytic anemia, treated with digoxin, diuretics and procaine amide.

Physical examination and chest x-ray confirmed the presence of congestive failure and pulmonary edema. BUN was elevated and creatinine normal. She was treated with digoxin, furosemide, salt restriction, and bed rest. With the exception of her rising BUN and creatinine, she did well.

Thirty days after admission, a 5 pound, 13½ ounce healthy male infant was delivered by cesarean section. The patient's postoperative course was characterized by worsening heart failure.

She became more dyspneic with increasing BUN (Fig. 1). Five days after delivery she became cyanotic, disoriented, and developed Cheyne-Stokes respirations with severe proteinuria. Pulmonary edema became worse and apneic spells became longer. Her operative incision separated and was reclosed. On the eleventh day post "C" section the patient was only semiconscious. She became jaundiced and developed the murmur of mitral insufficiency. Fibrinolysis developed with a platelet count of sixty thousand and a fibrinogen of 127 mg%. Prothrombin time was control 12, patient 15, and PTT was normal. Transfusion and epsilon amino caproic acid were used to control her coagulopathy. High dose steroids were added. Although her blood pressure remained 100 mm Hg, the patient was rapidly deteriorating, with cerebral, liver, renal, cardiac and pulmonary failure in spite of maximal medical management. Intra-aortic balloon pumping was started the 14th day with a 40 cc Avco intra-aortic balloon catheter inserted through the right femoral artery using local anesthesia. Systemic heparinization was not used.

Postoperatively, mixed venous oxygen saturation rose immediately from 40 to 58%. Epsilon amino caproic acid was continued. With a digoxin level of 2.8 micrograms she developed multiple arrhythmias, including both supraventricular arrhythmias and ventricular fibrillation. Multiple drugs and cardioversion were required. Her mental status returned to normal over the next two days. Steroids were tapered and her coagulopathy resolved. Hyperalimentation was started. The BUN fell rapidly after a single dialysis and remained low. After 22 days the renal and liver failure had resolved, her pulmonary edema had cleared somewhat, and her mental status had become normal. Attempts to wean

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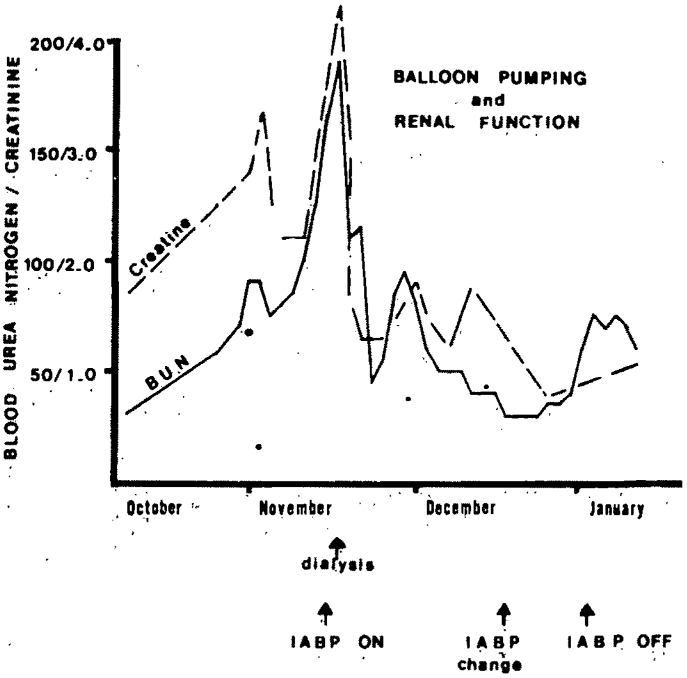


FIG. 1. The effect of intra-aortic balloon pumping on BUN and creatinine. Intra-aortic balloon pumping sustained a pronounced decrease in BUN and creatinine.

her off the pump were made over several days, but when the assist interval was reduced to 1:4 she became confused and disoriented and 1:1 pumping was resumed. Mental clarity returned. The balloon catheter tube developed a leak and was repaired using silastic bathtub caulking and plastic tubing. Our practice of having the patient sit in a chair undoubtedly contributed to the tube failure.

Ischemia of both lower extremities developed and heparin was started. Arteriogram the following day showed pronounced clot formation around the catheter and in both legs (Fig. 2). The catheter was removed and a new one placed in the left femoral artery. Clots were removed from the aorta and both femoral arteries using Fogarty catheters. Postoperatively, pedal pulses were restored and profuse diuresis ensued. Systemic heparinization was instituted until the following week when significant bleeding developed from the suture line requiring reoperation and one additional suture. Aspirin and dipyridamole were used from that time. Cardiac catheterization showed severe left ventricular dysfunction. No coronary artery or valve pathology was found. LVEDP was 34 and cardiac output on the pump was 2.2 L/M. With the discontinuance of the intra-aortic balloon pump LVEDP was 44 and C.O. 1.8 L/M.

Since clots were seen in the arm vessels, she was weaned from the balloon pump over the next several days. She became disoriented, with absent peripheral pulses, little blood pressure and severe metabolic acidosis. Severe clotting in her peripheral vessels precluded further balloon pumping, so the catheter was removed, and clots were removed from her aorta and left femoral artery using Fogarty catheters. Postoperatively, shock and metabolic acidosis resolved, and confusion cleared. Cardiac compensation remained marginal on maximal therapy until her transfer to a local hospital where she died 3 weeks later of intractable congestive failure. No autopsy was obtained.

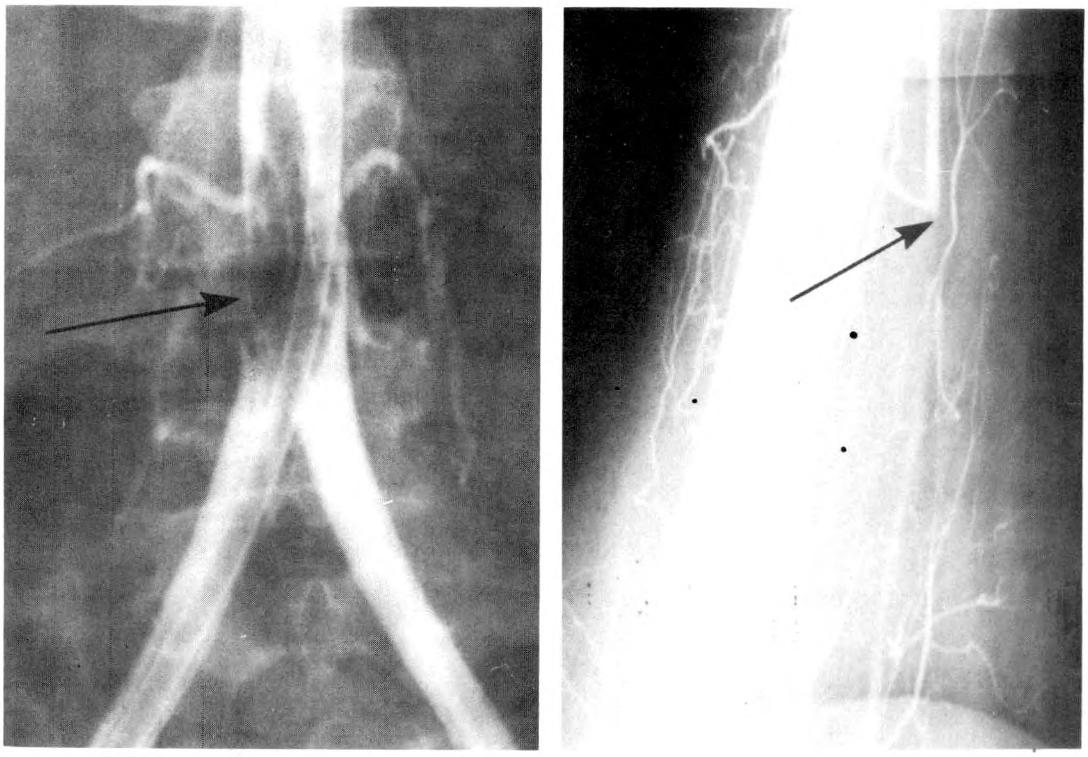
Discussion

Perinatal cardiomyopathy is an unexplained development of cardiomegaly and congestive failure during pregnancy or within 3 to 4 months following its termination. No previous cardiac disease is usually present.[1,4,6,9,10,12] The condition is often fatal, carrying a mortality of 30 to 60 per cent. Affected patients die of intractable congestive heart failure, arrhythmia, or embolization. Symptomatic medical therapy seems to have little effect on the course of the disease. No specific therapy, other than cardiac transplantation, is currently available.

The etiology of this disease is unknown. Nutritional deficiency, infections and auto-immune process have been implicated.[4] Treatment has been largely symptomatic with dietary deficiencies corrected and prolonged bed rest.[5]

Many authors have emphasized the variable nature of this disease. Although the mortality is high, some patients recover entirely.[1,10] DeMakis et al.[6] divided their patients into two groups. The first, though initially quite ill, recovered a normal-sized heart within 6 months. Their prognosis was good, though 5 of 8 who had subsequent pregnancies had mild recurrences of the disease. The second group, sometimes showing transient improvement, retained cardiomegaly. Eighty-five per cent of these patients eventually died of intractable congestive failure. In more severly and acutely ill patients, the intra-aortic balloon pumping may be used to further reduce the afterload on the diseased heart in an attempt to improve the advanced cardiac failure.

Intra-aortic balloon pumping often produces the same dramatic relief of cardiogenic shock in patients with myocardial infarction as it did in the patient reported. The physiologic mechanisms for this improvement have been carefully documented.[3,7] Not only does the balloon pump increase cardiac output, but it also increases coronary perfusion. By decreasing the afterload on the left ventricle, ventricular work is decreased as much as 25%. Most of these physiologic benefits apply as well to the heart failing because of cardiomyopathy. Increased cardiac output was undoubtedly responsible for the prompt resolution of hepatic, renal, pulmonary and cerebral failure in this patient. With other systems failing because of poor peripheral perfusion, increasing acidosis and hypoxia also aggravated cardiac decompensation.[11] Increasing stroke volume and relief of ventricular work could "buy time" for possible recovery of myocardial function. Since many of the physiologic benefits to the myocardial infarction, septic shock[2] and cardiomyopathy patients are the same, the dramatic initial response can be expected. Each of these problems requires a relatively brief period of support before either type of patient recovers or expires. Lack of an endpoint and the potential need for long term support are undoubtedly the reasons balloon pumping has not previously been applied to the other major cause of cardiogenic shock—cardiomyopathy.



FIGS. 2a and b. Aortogram showing clot formation around intra-aortic balloon catheter and in the right leg (arrow).

Little is known about the time limits of intra-aortic balloon pumping. How long can the pump be left in place without life-threatening complications? Is there a time beyond which pumping cannot be expected to produce long term benefit to the patient? Many complications have been associated with balloon pumping. We have seen infections, thrombosis, ischemic legs, bleeding, and false aneurysm formation. During this 7 week "pump run," the patient's main problems were thrombotic, necessitating removal of the first balloon catheter at 32 days, and the second at 49 days. Though it has not been our routine to use anticoagulation therapy on these patients, anticoagulation was begun when the second catheter was inserted. Bleeding required discontinuation of heparin, but aspirin and dipyridamole were continued until thrombus formation required removal of the second catheter. There was no evidence of balloon failure and helium leak during this long pump run. The consequences of thrombus formation were easily controlled using Fogarty catheters. Our experience with this patient shows that safe pumping can be carried out for as long as 7 weeks.

During its evolutionary phase, pumping was carried out for only 24 hours before the patient was considered pump dependent. We have been more persistent with this form of assist than many because some of our patients on the balloon pump up to 3 weeks have benefited. With this philosophy, dependence has not been a problem. Although we have enough survivors to justify pumping until a complication or catastrophe ensues, the question of a time limit beyond which there is no long term benefit remains unanswered. This patient received no long term benefit although she was discharged with improvements in the hemodynamics and concurrent "normalization" of multi-system failures.

Conclusion

Long term intra-aortic balloon pumping was carried out in a patient with perinatal cardiomyopathy and cardiogenic shock to provide sustained benefit by preventing advanced cardiac decompensation with secondary hepatic and renal failure. The patient's condition was improved during the period of assist and the feasibility of balloon pumping for as long as 7 weeks was demonstrated. Whether this type of treatment is recommended for all cardiomyopathies needs further therapeutic evaluation.

Addendum

Since submission of this report, a 54-year-old Caucasian man, who arrived at Denver General Hospital in ventricular fibrillation due to cardiomyopathy, was resuscitated into cardiogenic shock and assisted with the balloon pump for 6 days. Following discharge from the hospital he did well for a month when he had another episode of ventricular fibrillation from which he could not be resuscitated.

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Carcinoembryonic Antigen (CEA) as a Prognostic and Monitoring Test in Clinically Complete Resection of Colorectal Carcinoma

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The prognostic and postoperative monitoring capabilities of the CEA assay were compared to pathological staging of the operative specimens, clinical followup including endoscopy, radiology and scanning techniques, as well as DNCB skin testing and laboratory enzyme determinations (alkaline phosphatase and transaminase). A total of 46 patients with curative resection for colorectal carcinoma were studied. This included 23 patients with recurrent tumors compared to 23 long-term survivors without signs of recurrence at the time of the study. Preoperative CEA determinations were a good prognostic tool comparable to pathological staging of the specimen. Postoperative CEA monitoring was the earliest sign of recurrence in 14 of 23 patients and was positive at the time of recurrence determined by other methods in 20; it was negative in only three cases. The incidence of false positive results among the non recurrent group became a lesser problem when repeated elevated values were required before considering the patient as having a recurrence. From these data, it seems reasonable to propose the use of a second-look operation in patients with maintained elevation of circulating CEA and no clinical signs of tumor presence, if we are to treat recurrence at an early stage. Chemotherapy would be an alternative way to deal with this problem, since the absence of clinical signs in general correlate with small bulk of tumor which at this time may be more susceptible to chemotherapeutic agents.

CARCINOEMBRYONIC ANTIGEN is a tumor-associated antigen identified in colorectal carcinoma tissue in 1965 by Gold and Freedman.[4] This discovery was followed by a search for this antigen in patient's sera which succeeded when Thomson and co-workers[17] described a method to detect nanogram quantities of the antigen in the serum of patients who have tumors of the digestive tract. The method was further elaborated [2,5] and evaluated in patients with other cancers and noncancerous diseases. Initially thought to be specific for colorectal cancer, it soon became obvious that elevation of this circulating antigen was present in several different malignancies as well as in some non-malignant diseases.[8,12,15] A larger clinical experience has been accumulated since and the significance of the test as a diagnostic tool in colorectal carcinoma has been defined in part at least by cooperative studies.[6,13]

The prognostic value of preoperative determinations as well as postoperative monitoring to diagnose recurrence, progression or regression for a number of tumors has also been discussed by several authors.[1,3,7,9–11,18] The present study was undertaken in order to assess for colon cancer: 1) The value of preoperative CEA as a prognostic tool, 2) Its correlation to tumor staging using a TNM and Duke's classification, 3) The usefulness of postoperative monitoring with periodic CEA determinations, 4) The correlation of CEA with other clinical and laboratory tests.

Materials and Methods

The records of 271 patients with histologically proven colorectal carcinoma were reviewed. A total of 66 patients had complete resection with preoperative and postoperative CEA determinations over a period of time longer than 6 months. All patients with a second primary occurring at any time during the period of observation were excluded from the study. These patients had one preoperative and one postoperative determination at 4 days, 2 weeks, one month and then every 3 months, except for those patients undergoing additional treatment

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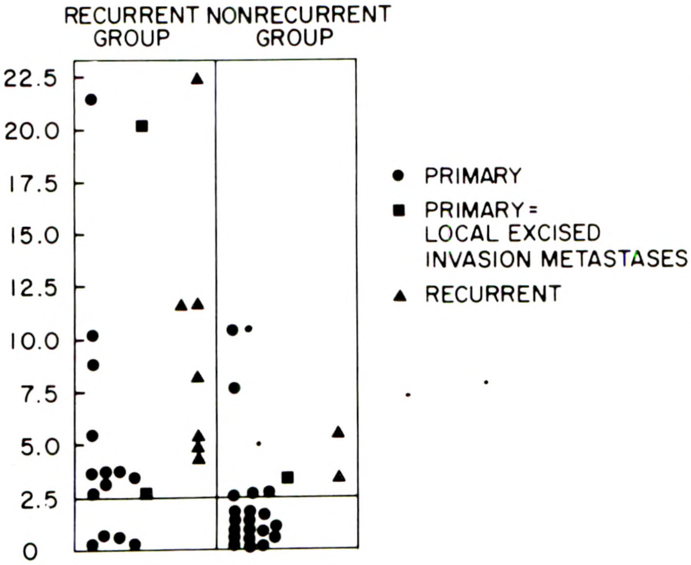

FIG. 1. Nineteen of 23 patients who developed recurrence had CEA values above 2.5 ng/ml as opposed to 8 among the 23 control patients.

such as radiation or chemotherapy in which case, they were tested on a monthly basis. The method used was that of Hansen as described by Chu and Reynoso.[2]

Among the 66 patients with clinically complete resection, a total of 23 developed metastatic or regional recurrence. This group of 23 patients was compared with a group of 23 patients clinically free of disease which included all the patients without recurrence and a followup longer than 14 months at the time of this report. The patients who did have recurrence did so between three and 21 months post resection, with only one developing recurrence after 18 months. The non-recurrent patients had preoperative and postoperative CEA determinations and their postoperative followup period ranged between 14 and 46 months with a mean value of 25 months with only 4 patients having less than 18 months followup. The 23 patients from the recurrent group consisted of 10 men and 13 women with ages ranging from 41 to 81 and a mean of 63 years. The mean age for the non recurrent group was also 63 years with a range from 28 to 86. There were 8 men and 15 women in this group.

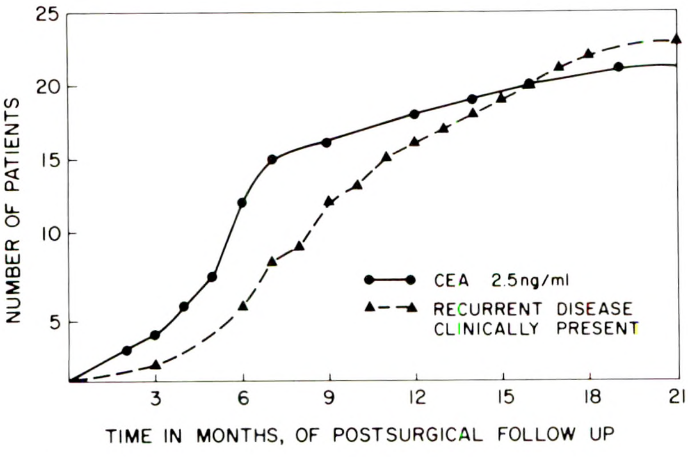

Fig. 2. Following curative resection, CEA usually is elevated in patients developing recurrence 3½ months before disease is clinically evident.

Results

Preoperative CEA Values

In 19 of 23 patients (83%) who underwent curative resection, but later developed recurrence, the preoperative CEA values were above the levels considered as normal, or 2.5 nanograms per cc (Fig. 1).

Only 8 patients had preoperative elevations among the 23 patients in the non recurrent group and only three of these were above the 4 nanogram mark as compared to 14 from the recurrent group. It should be mentioned that two of these patients from the non recurrent group already had recurrent disease when entered into the study prior to resection so that it is likely that their tumor may still recur again. The mean CEA value for the recurrent group is 9.7 ng/ml while for the non recurrent group it is 2.5 ng/ml with a t value of 2.242, for the difference between the means of indicating a statistically significant difference at the 1% level.

Postoperative CEA Values

Twelve patients from the recurrent group and 20 from the non recurrent group demonstrated CEA levels within the 12th postoperative week which were above the preoperative values, while for 8 among the recurrent and 2 among the non recurrent patients CEA fell to levels below the preoperative ones. In the majority of patients, the values of CEA were stabilized by the 12th postoperative week.

An elevation above normal which persisted was present in 20 patients who developed recurrence, at the time of recurrence (87%) and became later elevated in one. In another patient, the CEA was low at the time of a small perineal implant which was resected with all later values still negative and the continued absence of clinical evidence of disease. The last patient from the recurrent group, although he had high preoperative values, never did show a rise in his serum antigen levels after abdominoperineal resection despite evidence of pulmonary metastases three months postoperatively.

Fig. 2 shows the mean time of detectable rise in CEA for all those patients in whom disease recurred. The mean lead time is a little more than 3 months. We also note that two patients never did show an elevation as discussed above.

Among the 20 patients with elevated values at the time of recurrence, 14 had their values abnormally elevated more than 3 months before clinical detection of metastases. For those 14 patients, there is a significant 5½

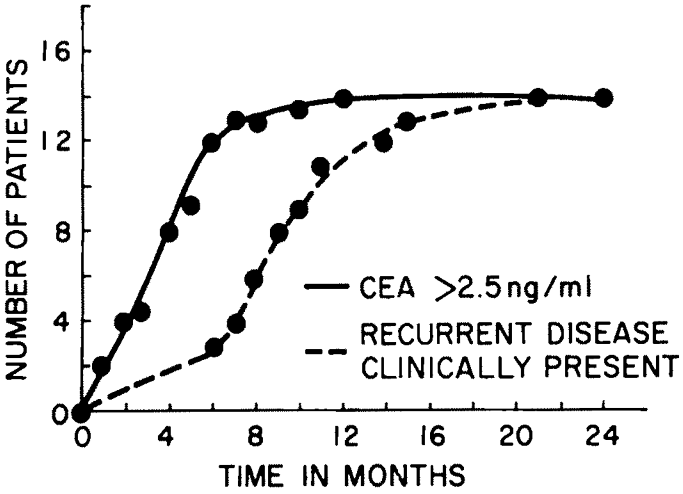

FIG. 3. Following curative resection 14 of 23 patients demonstrated a rise in CEA more than 3 months before recurrence was otherwise detected.

months lead time in detection of recurrent tumor as against other clinical means of detection (see Fig. 3).

In the non recurrent group of patients, there is one patient whose postoperative values were all positive and who had a repeatedly negative work-up for signs of recurrence. This patient is a chronic and heavy smoker. One patient has had very irregular values over a followup period of 31 months with no evidence of recurrence to date. Her liver disease was established by examination with an elevated alkaline phosphatase and SGOT. There are 4 other patients with transitory elevations of 2 and 3 (2 of these had 3 consecutive elevated values) consecutive CEA values who have later become negative for a prolonged period of time and who remain without evidence of disease at present. There are 4 additional patients who demonstrated a single isolated value which was elevated, but in whom a repeat value was normal. (A total of 278 determinations have been done in the 23 patients in whom disease has not recurred.) The remaining 13 patients in the non recurrence group never showed an elevation of CEA subsequent to the 12th postoperative week.

Disregarding the isolated elevations, we still have 6 patients (out of the 23 non recurrent individuals) with false positive results. Two of these have clear cut associated benign cause for these elevations and of the other 4, 2 were elevated over a span of 3 values.

Considering those patients in the two groups together who could be staged, there were 12 patients with recurrent or metastatic disease (Duke's D) at the time of clinically complete resection; 11 of them had elevated preoperative CEA values and nine of them have developed recurrence to date (Tables 1 and 2).

Seventeen patients who had nodal metastasis (Duke's C) had elevated CEA values in 8 of 11 who recurred and

TABLE 1A. *Extent of Disease and Antigen Level in Recurrent Patients*

Disease Stage and Preoperative CEA			
Localized (Duke's A&B)	Nodal Involvement (Duke's C)	Local Recurrence (Duke's D)	Metastases (Duke's D)
TNM vs CEA	TNM vs CEA	TNM vs CEA	TNM vs CEA
T3 1.4	T2N1 0.5	T4 (R)* 7.1	T3N2M1 2.5
T4 3.3	T3N1 4.6	T4(R) * 8.5	T4N2M1 21.8
T4 4.3	T3N1 4.6	T4 (R)* 11.3	M1 (R)* 4.0
	T3N1 13.1	T4 (R)* 128.3	M1 (R)* 5.1
	T3N2 2.8		M1 (R)* 10.8
	T3N3 0.0		
	T3N3 9.4		
	T4N1 3.9		
	T4N1 5.0		
	T4N1 27.0		
	T4N2 0.0		
Mean: $\bar{x}=3.0$	$\bar{x}=6.0$	$\bar{x}=38.8$	$\bar{x}=9.0$

*(R) Recurrent disease from previously resected Colorectal carcinoma.

TABLE 1B. *Extent of Disease and Antigen Level in Non Recurrent Patients*

Disease Stage and Preoperative CEA			
Localized (Duke's A&B)	Nodal Involvement (Duke's C)	Local Recurrence (Duke's D)	Metastases (Duke's D)
TNM vs CEA	TNM vs CEA	TNM vs CEA	TNM vs CEA
T1 0.0	T2N1 0.3	T3 (R)* 0.3	T4N1M1 4.0
T2 0.5	T2N1 0.4	T3 (R)* 6.4	
T2 0.5	T2N1 2.0		
T2 0.6	T3N1 0.6		
T2 1.2	T3N1 0.8		
T3 1.7	T4N1 2.5		
T3 0.0			
T3 0.9			
T3 1.7			
T3 1.8			
T3 2.7			
T3 4.0			
T3 8.0			
T3 12.8			
Mean: $\bar{x}=2.7$	$\bar{x}=1.1$	$\bar{x}=3.4$	$\bar{x}=4.0$

*(R) Recurrent disease from previously resected colorectal carcinoma.

TABLE 2. *Recurrence of Disease in Patients After Complete Resection of Colorectal Carcinoma as Compared to Their Extent of Disease and Preoperative CEA Levels*

	Total No. Patients	Preoperative CEA > 2.5
Localized Tumor (Duke's A & B)	17	6
Recurrence	3	2
Nonrecurrence	14	4
Nodal Metastasis (Duke's C)	17	9
Recurrence	11	8
Nonrecurrence	6	1
Recurrent and Metastatic (Duke's D)	12	11
Recurrence	9	9
Nonrecurrence	3	2

TABLE 3. *Alkaline Phosphatase and SGOT Monitoring*

RECURRENT GROUP	#Patients
Always normal (failed to elevate)	16*
Elevated at the time of metastases	4
Elevated before evidence of metastases	3
Elevations within 6 weeks of major surgery as well as isolated elevations followed by normal values were eliminated.	
NON RECURRENT GROUP	
Always low (normal)	5
Isolated elevation	8
Temporary elevation	5†
Permanent elevation	5
Elevations within 6 weeks of major surgery excluded	

*In three patients of this group there was an elevation several months after obvious recurrence.

†Two or more consecutive elevated values with later return to normal.

in only one out of 6 who did not recur. There were 17 patients with localized tumors (Duke's A and B) 3 of whom developed recurrence (two with elevated CEA), while 4 of 14 who did not recur had abnormal values. There is a clear increased incidence of elevated values as disease stage progresses with 11 of 12 patients seen initially with recurrent or metastatic disease having elevated plasma values.

DNCB Skin Testing

A total of 14 patients of the recurrent group who had not been previously sensitized and 13 of the non recurrent patients were skin tested with 500 micrograms of an acetone solution of DinitroChloroBenzene (DNCB). There was no significant difference in delayed hypersensitivity response between the two groups either preoperatively or postoperatively. In these patients with technically curatively resected colorectal carcinoma, the DNCB skin-test results as performed by us at the time of the study do not correlate with the stage of tumor (TNM) or with serum CEA levels.

Alkaline Phosphatase and SGOT in the Postoperative Followup

Elevations of alkaline phosphatase and SGOT occurring within 6 weeks of major surgery were disregarded. Single isolated elevations follow by normal values when repeated were also excluded. Among the 23 patients with recurrence, 16 had normal values at the time of obvious evidence of metastases, but three of the 16 turned positive at 3, 4 and 5 months post-recurrence respectively (Table 3). In four patients, the alkaline phosphatase was elevated at the time of recurrence and in only three others, it preceded the clinical evidence of metastases (two occurring in the liver and one in the abdominal wall). Interestingly, in these three patients in whom the alkaline phosphatase or the SGOT were elevated before recurrence, this elevation occurred earlier than the CEA elevation in each instance. In the non recurrent group of patients, alkaline phosphatase and SGOT were always low in only 5 of 23 patients. In 8 patients, there were single occasional elevations of either one or both enzymes with later return to normal values. In 5 patients, one or both enzymes has been elevated in all determinations without any manifestation of recurrence, while in the remaining 5 individuals, there were temporary consecutive elevations with later return to normal enzyme values. The enzyme values did not correlate with our CEA results, and correlated poorly with the disease state (Table 3).

Discussion

Our findings demonstrate the usefulness of the CEA assay when used preoperatively for estimating prognosis in colon cancer and for the prompt recognition of recurrence during postoperative monitoring of those patients who have undergone clinically complete resection for this malignancy. In general, patients with more advanced disease have a poorer prognosis and higher CEA levels. This agrees with previous reports by Holyoke,[7] Lo Gerfo[9] and their co-authors. CEA correlates well with TNM and Duke's staging of tumor, but CEA is usually superior to staging as a prognostic reference. In addition it is easier to perform, faster and more economical.[14] When monitoring resected patients for prompt recognition of recurrence, the CEA assay is usually superior to other available techniques when used in conjunction with endoscopy, biopsy and radiology, as was found by McCartney.[11]

We found no correlation between transient CEA elevations and clinical recurrence, but persistent or increasingly elevated levels meant the presence of metastases, except for two patients in the non recurrent group who although without clinical evidence of metastases at present, are suspected of bearing sub-clinical amounts of neoplasia. These findings correspond with those of Sorokin et al.[16]

Our data suggest that between 3 and 18 months, 3 successive elevations of CEA showing a rise gives a better than 90% certainty of the presence of recurrent disease and in appropriate patients would perhaps justify second look or other therapy. Single values are not reliable and even two successive elevated values may be misleading in 20% of patients. We recommend that if an elevated CEA value is encountered, the test should be repeated at 10 day to 2 week intervals, if necessary times two.

If our current data continue to be valid, an initial CEA value greater than 4.5 ng/ml will predict a greater than 80% chance of recurrence within 18 months of resection so that this parameter may turn out to be useful in the future as a means of deciding on adjuvant therapy.

Alkaline phosphatase and SGOT correlate poorly with presence or absence of recurrence when used to monitor resected patients. When these enzymes are used to monitor colon cancer patients for recurrence, the frequency of both false positive and false negative results is much higher than is the case for CEA. Postoperatively CEA proved to be an excellent monitor, detecting 20 of 23 recurrences at the time of clinical diagnosis of recurrence and in 14 patients preceding clinical diagnosis of recurrence by any other test by more than 3 months.

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Parotid Space Tumors of Non-salivary Origin

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A review of 700 parotidectomies showed that 98 procedures were performed for parotid space tumors of non-salivary origin. The clinical presentation in this group of patients did not differ significantly from the larger group of salivary tumors except for a higher incidence (12%) of the former in the younger age group. Of the 98 cases, 54 proved to be lymph node tumors, both neoplastic and inflammatory and 44 were tumors of various somatic origins. Among the latter group, bone and joint tumors, vascular lesions and some connective tissue tumors may be recognized preoperatively. Generally, however, the entire group of non-salivary tumors can be distinguished only intra-operatively, if at all. Correct recognition may lead to variations in operative techniques and extent of resection.

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IN ANY LARGE SERIES of parotidectomies a number of cases will always be found in which the tumor occupying the parotid space originated in other than salivary tissue.[1] However, these cases are rarely reported as a group, the literature containing chiefly individual case reports or analyses of a single histopathological entity.[5,8]

We have reviewed our own experience of approximately 700 parotidectomies and have collected 98 cases in which the tumor was of non-salivary origin. This group of tumors therefore represents 14% of the total number for which parotid surgery was undertaken.

Anatomy

The anatomic borders of the parotid space are the external auditory canal and mastoid tip posteriorly, the zygomatic arch superiorly and the ascending ramus of the mandible and the masseter muscle for a variable space anteriorly. Inferiorly the "tail" of the parotid extends below the angle of the mandible and the mastoid tip into the neck. In depth the so-called "deep lobe" of the parotid occupies the retromandibular space, resting upon the styloid process which separates it from the retrotonsillar region.

Masses within this space are almost always diagnosed as salivary gland tumors. Although these are statistically the most frequent there are many other structures within and traversing the parotid space which can give rise to tumors which will mimic the more common ones of parotid origin.[7]

It is important that the operating surgeon be aware of the existence and nature of these tumors because such recognition may: 1) alter his surgical approach and 2) influence the extent of resection called for.

In some instances, the correct diagnosis can at least be suspected preoperatively. In the majority, however, the nonsalivary nature of these tumors can be determined only at the time of surgery. The surgeon must therefore be prepared to recognize the true nature of these tumors and, if necessary, vary his operative procedure as indicated below in order to insure optimal surgical management.

Pathology

Our 98 non-salivary tumors could be classified on the basis of their histopathology as follows: tumors arising in (intraparotid and periparotid) lymph nodes: 54 (Table 1); Tumors of somatic origin: 44 (Table 2).

Clinical Presentation

Analysis of these cases in terms of age, sex and the presence of symptoms revealed no significant differences when compared with similar analysis of our group of patients whose tumors originated in the parotid gland itself, except with respect to age: 12 of our 98 tumors (12%)

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were found in patients under the age of 20. Fewer than 5% of salivary gland lesions occur in this range.[2–4,6] The breakdown of these 12 cases in terms of etiology is shown in Table 3. With respect to clinical presentation, for the entire group of parotid tumors, almost all came to attention because of the single symptom of a mass in the parotid area.

Discussion

Lymph Node Disease

It has been our experience that in the preoperative evaluation of a parotid tumor, it is almost impossible to differentiate lesions originating in lymph nodes from those of true salivary origin. None of the patients under discussion in this category had lymphadenopathy detectable elsewhere than in the parotid area. Certainly, if such is the case, one would not approach that parotid area first to establish the diagnosis. Similarly, those patients whose parotid tumors proved to be metastatic in nature never had an overt metastasis elsewhere in this series.

Surgical Management When Tumor Is Discovered to be of Lymphoid Origin

When enlarged periparotid lymph nodes are found and the salivary gland itself is seen to be intact, it is our experience that it is not always necessary to perform a parotidectomy. It is usually possible to enucleate the nodal tissue only, providing one has adequately identified the facial nerve divisions close to the node. Fortunately these nodal enlargements tend to occur at the "tail" (vide supra) of the parotid. In these circumstances, procedurally, the surgeon should first identify the posterior facial vein and trace this superiorly. Careful dissection of this structure will lead him to the cervical and submandibular divisions of the facial nerve. These are found crossing the vein on its superficial surface. By identifying and protecting the nerve branches it is not difficult to remove safely the lymph gland alone.

TABLE 1. *Tumors Arising in (Intraparotid and Periparotid) Lymph Nodes*

A. Neoplastic		
1. Primary		
Malignant lymphoma		16
2. Metastatic		
Melanoma	(2)	
Colonic ca	(1)	
Tonsillar	(1)	
Lymphoepithelioma	(1)	
Total metastatic neoplasm		5
B. Inflammatory		
Hyperplastic lymph nodes	(19)	
Tuberculosis	(8)	
Actinomycosis	(1)	
Infectious mononucleosis	(1)	
Cat scratch fever	(1)	
Sarcoidosis	(2)	
Toxoplasmosis	(1)	
Total inflammatory		33
Total (Lymph node disease)		54

TABLE 2. *Tumors of Somatic Origin (44)*

A. Skin and appendages		
1. Benign		
Epidermoid inclusion cyst		2
Sebaceous lymphadenoma		1
Branchial cyst		1
2. Malignant		
Sebaceous gland carcinoma		1
Total skin	(5)	
B. Muscle and connective tissue origin		
1. Benign		
Lipoma		18
Fibroadenoma		1
Desmoid tumor		1
Granular cell myoblastoma		1
Hypertrophy masseter muscle		1
2. Malignant		
Fibrosarcoma		1
Myxosarcoma		1
Total muscle and connective	(24)	
C. Vascular origin		
Hemangioma		4
Venous aneurysm		1
Cystic hygroma		1
Total vascular	(6)	
D. Neurogenic origin		
Neuroma facial nerve		1
Neurofibroma		2
Meningioma		1
Total neurogenic	(4)	
E. Bone and joint origin		
Ameloblastoma		1
Vilonodular synovial sarcoma		1
Osteochondroma		2
Aneurysmal bone cyst		1
Total bone and joint	(5)	
Total Somatic Tumors	(44)	
Total Lymph Node	(54)	
Total Tumors of Non-salivary Origin	(98)	

When the involved lymph node is intraparotid however, the correct diagnosis cannot be made even at surgery. The operative procedure then must be the same as for a salivary gland tumor. All of these intraparotid lymph nodes in our experience have been found in the superficial "lobe" of the parotid. Complete removal of the superficial lobe under these circumstances is exactly similar to the procedure used for salivary tumors: the first step is identification of the facial trunk by using the bony landmarks. Next, the superficial portion of the parotid gland is excised *en bloc* with preservation of its capsule and avoidance of the facial nerve branches. As with tumors of salivary origin no attempt is ever made to extract the tumor from the salivary gland proper.

TABLE 3. *Etiology of Tumors in Patients Less Than 20 Years of Age*

Reactive lymph nodes		2
Inflammatory lymph nodes		3
Infectious mononucleosis	(1)	
Tuberculosis	(1)	
Non-specific granuloma	(1)	
Skin Tumors (epidermoid cysts)		2
Masseter muscle hypertrophy		1
Bone tumor—benign		1
Vascular—hemangioma		1
Malignant tumors		2
Fibrosarcoma	(1)	
Myxosarcoma	(1)	
Total		12

Somatic Tumors

Among the somatic tissue tumors are some for which a correct preoperative diagnosis can be made or, at least, suspected. The epidermoid inclusion cysts and sebaceous adenoma included in our series were attached to the skin inside the external auditory canal: closer preoperative inspection might have yielded a clue. Similarly, masseter muscle hypertrophy can usually be distinguished by correct physical examination; however, in the one case included in our series we were fooled.

We were not able to distinguish preoperatively lipomas with any consistent degree of success. On a few occasions the correct preoperative diagnosis was considered because of the palpatory characteristics.

The four hemangiomas in our series all were of the cavernous ("adult") type without changes in the overlying skin. There are typical clinical features in this condition which can be used to make a correct diagnosis. These are: 1) increase in size with straining and leaning over; 2) compressibility; and, 3) x-ray evidence of microcalcification. These diagnostic features will be elaborated upon in a separate report.

The last group, bone and joint tumors, can be suspected by their hardness and can usually be confirmed radiologically if one includes sialography. Despite this, we have not been able to make the correct histological diagnosis easily, especially in the unusual tumors in our series.

Surgical Application

By correctly recognizing that a given tumor is of lymph node rather than salivary origin the operating surgeon can frequently limit the extent of his resection and simplify the procedure as outlined above. This holds true for both primary and secondary lymphatic tumors, as well as most inflammatory diseases. Somatic tumors on the other hand are less likely to respect the border of the parotid capsule and surgical excision may have to be extended beyond the "usual" confines of parotidectomy. In such cases, it is imperative that identification and preservation of the facial nerve be carried out prior to resection. Indeed, it is precisely those cases in which unusual tumors are present—where direction of growth cannot be adequately predicted and where malignancy is more likely—that the surgeon must establish precisely the location and possible involvement of the facial nerve. He must arrive at this decision *before* embarking upon resection of the tumor. In our opinion only bony landmarks, consisting of the mastoid tip, external auditory canal and styloid process can consistently be relied upon to lead the surgeon to the facial trunk quickly and without risk.

Summary

Of approximately 700 parotidectomies in our experience, 98 were performed for parotid space tumors of nonsalivary origin. Among these 98 cases were 54 involving intraparotid and periparotid lymph nodes and 44 tumors of various somatic origins. We have discussed the characteristic clinical features and the considerations which lead to correct intraoperative identification. Such accurate recognition influences greatly surgical judgement and the postoperative result.

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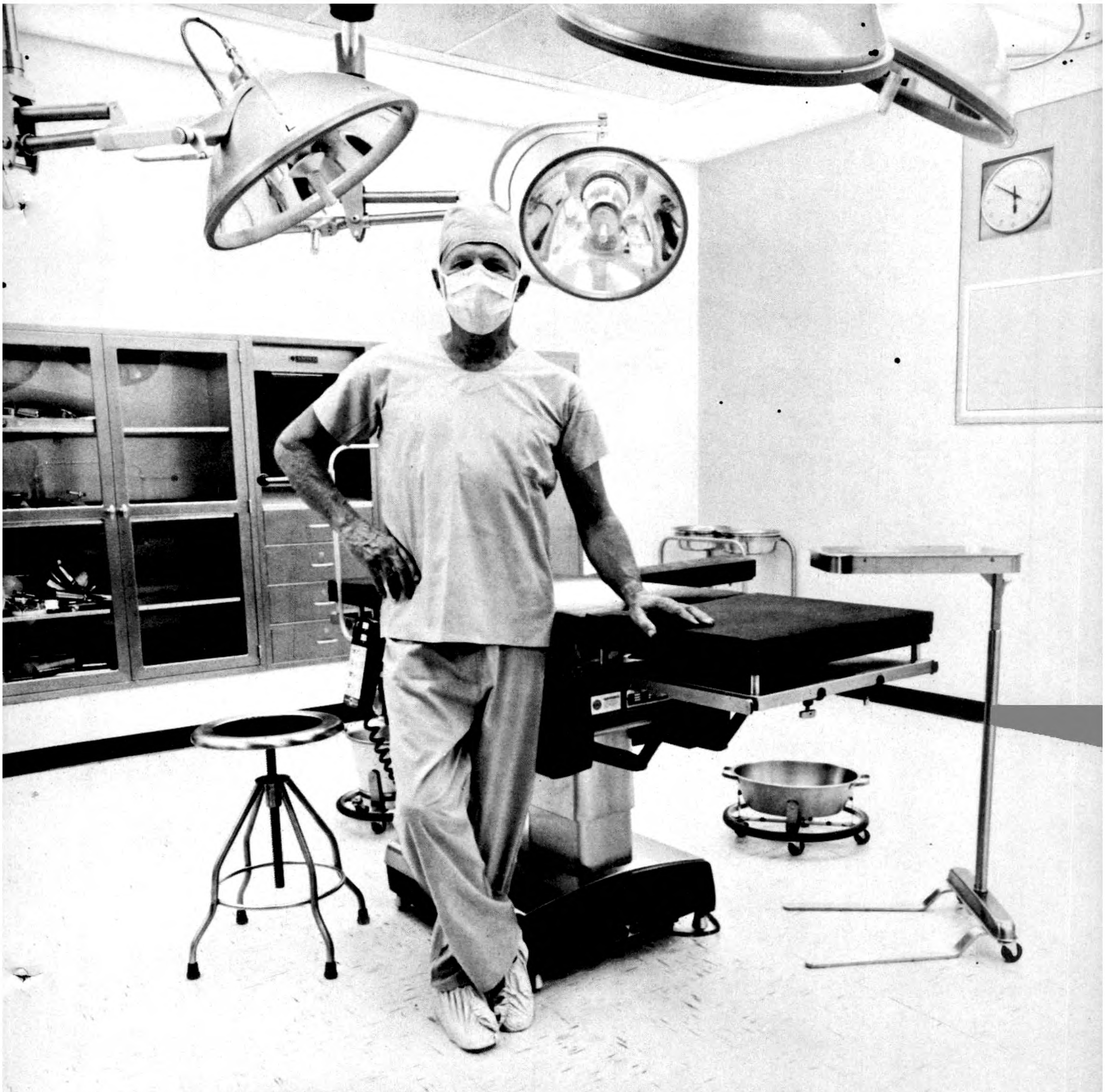

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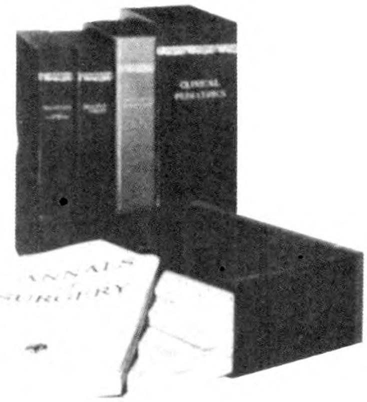

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Indianapolis, Indiana 46206

500390

Relief from her postsurgical pain

Darvocet-N® 100
100 mg. propoxyphene napsylate and
650 mg. acetaminophen

contains no aspirin

**Darvon®
Compound-65**
65 mg. propoxyphene hydrochloride, 227 mg. aspirin,
162 mg. phenacetin, and 32.4 mg. caffeine

contains aspirin

for mild to
moderate pain

See summary of prescribing information on adjoining page.

P. 24,771

Upjohn

Anaerobic GI flora–site specific

The gastrointestinal tract of man contains an abundance of microorganisms composed predominantly of anaerobic bacteria. The geographic location of these bacteria in the intestine may explain the different rates of infectious complications associated with injuries to different parts of the gastrointestinal tract. Soilage from the upper portion of the small bowel is usually associated with a lower rate of infection than from the lower small bowel and colon.

Intra-abdominal infections: Intra-abdominal infections may complicate penetrating abdominal wounds, particularly when the integrity of the bowel has been compromised. Such complications are frequently associated with trauma resulting from automobile accidents or criminal violence (such as gunshot wounds or stabbings). Anaerobic infections may occur as postsurgical complications. Peritonitis and abscess formation may cause particular problems. Intra-abdominal infections may also occur when bowel tissue becomes necrotic or nonviable as in cases of vascular compromise, embolic disease, obstruction, strangulation, toxic dilatation, and similar conditions characterized by tissue anoxia.

Appropriate therapy for the infectious complications is often a concern of many physicians.

...and how to manage them: The initiation of antibiotic therapy, particularly when peritonitis exists, may be a matter of immediate importance. In such emergency situations, the surgeon's selection of an antibiotic is frequently made on the basis of scant etiologic evidence. However, his knowledge of the specific normal flora in a given area of the bowel and how the flora can be altered by certain pathologic conditions will aid him greatly in his antibiotic selection.

Therapy which must be initiated presumptively may be chosen discriminatively: While inspection of Gram-stained specimens may prove useful, and cultures from the infection site will eventually provide valuable diagnostic information for the surgeon, the best clue to immediate antibiotic therapy may be the location of the infection. In the normal healthy adult, there is well-defined colonization by specific microorganisms in specific sites of the gastrointestinal tract. Thus a guide to the *normal* inhabitants of various areas may be helpful in suggesting the proper therapeutic agent.

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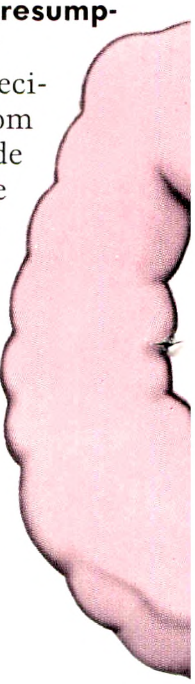
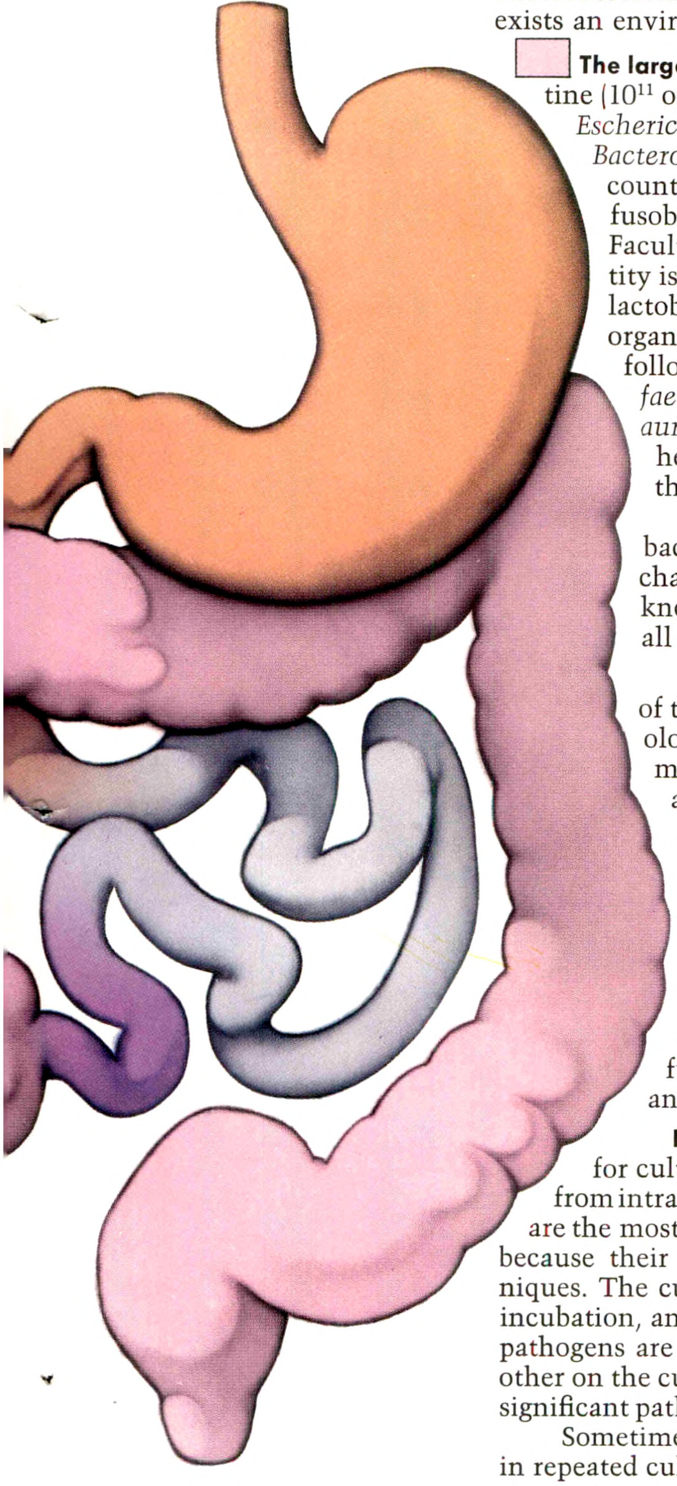


Guide to the normal adult intestinal microflora

🟧 **The stomach, and proximal and middle small bowel:** Here facultative enterococci, lactobacilli and anaerobes (originating in the oral cavity) exist in a concentration of 10^5 or less organisms per ml of contents. *Bacteroides fragilis* is virtually absent. Gastric acidity in this area limits the growth of many bacteria; therefore, most of the organisms are acid-resistant. In the middle portion of the small bowel there is sparse indigenous bacterial colonization, largely because of pronounced motility of this region.

🟪 **The distal small bowel:** In the ileum, enterococci and lactobacilli are seen in approximately the same quantities that occur in the stomach and duodenum. Coliforms are also observed—as are obligate anaerobes. *Bacteroides fragilis* and other fecal anaerobes first appear at this level. In fact, aerobic and anaerobic bacteria exist here in roughly equal proportions. The ileocecal valve, if functioning properly, provides a barrier against colonization by fecal anaerobes from the large bowel into this area. Beyond the ileocecal valve there exists an environment best suited to the proliferation of obligate anaerobes.



◻ **The large bowel:** Anaerobic microorganisms predominate the large intestine (10^{11} organisms per gram of contents). Obligate anaerobes outnumber *Escherichia coli* 1,000 to 10,000 to one in the large intestine, and *Bacteroides fragilis* is the anaerobic organism most frequently encountered. Other anaerobes, such as peptostreptococci, clostridia, fusobacteria, and eubacteria are also seen although not so profusely. Facultative aerobes are in the decided minority here, but their quantity is no less than elsewhere in the intestinal tract. Enterococci and lactobacilli are each present in concentrations of about 10^6 to 10^8 organisms per gram of contents. *Escherichia coli* is most common, followed by enterococci (*Streptococcus faecalis* and *Streptococcus faecium*), proteus, pseudomonas, and klebsiella. *Staphylococcus aureus* and *Candida albicans* are also present in the large bowel of healthy, normal individuals. The pathogenic potential of each of these microorganisms should never be overlooked.

Because the large bowel contains many different species of bacteria, disease or trauma in this area may present a special challenge. Accordingly, it is important to remember that no known single agent has proved to be uniformly effective against all of these organisms.

Variations in the normal microflora: The normal microflora of the intestinal tract may be substantially altered in certain pathological conditions. These alterations depend upon the patient's medical history and the nature of his present illness. If, for example, the patient has achlorhydria, tissue ischemia, reduced intestinal motility, blind loop syndrome or stasis, or has had previous antibiotic therapy or bowel surgery, significant changes in the microflora of the bowel may be observed. When gastric secretion, intestinal motility or anatomic integrity is altered, the flora of the small bowel may be affected. Under these conditions large numbers of facultative aerobes (e.g., *Escherichia coli*) and obligate anaerobes (*Bacteroides fragilis* and other fecal anaerobes) may be found in this area. A malfunctioning ileocecal valve could permit these aerobic and anaerobic bacteria to colonize the ileum.

Problems in diagnosis: Even though the methods currently used for culturing anaerobes have been greatly improved, bacterial cultures from intra-abdominal sites can be diagnostically misleading. Anaerobes are the most often overlooked category of potentially pathogenic organisms because their detection demands meticulous collection and culture techniques. The cultivation of certain anaerobes may require up to ten days of incubation, and even a brief exposure to air can kill many of them. Multiple pathogens are frequently encountered, and one organism can overgrow another on the culture plate. Blood cultures can be similarly deceptive, since all significant pathogens in a mixed infection are rarely isolated in a single culture.

Sometimes only the consistent reappearance of a given microorganism in repeated cultures is the clue to clinical importance.

Please turn page for information on one antibiotic of significance in the treatment of serious anaerobic intra-abdominal infections.

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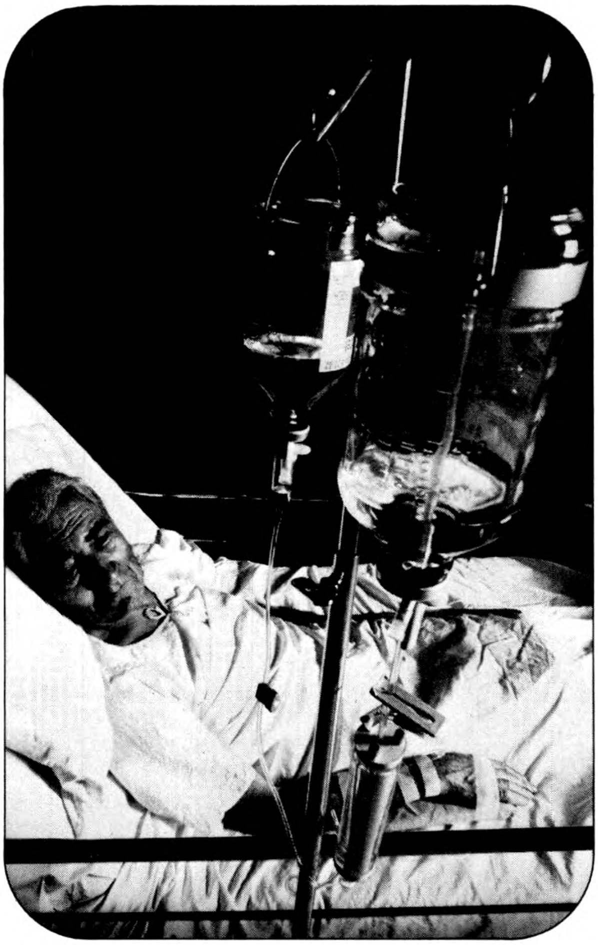
Therapeutic considerations...



Anaerobic activity: Cleocin® PO₄ (clindamycin phosphate injection) has proved to be effective in a variety of serious intra-abdominal infections caused by susceptible anaerobic organisms including gram-positive cocci, and gram-positive and gram-negative bacilli. Specifically, the activity of clindamycin has been established in the following conditions: septicemia; serious intra-abdominal infections such as peritonitis and intra-abdominal abscess; serious infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal-cuff infection caused by susceptible strains of bacteroides, fusobacteria, eubacteria, actinomyces, peptococci, microaerophilic streptococci, and clostridia.*

Since disc susceptibility testing with current methods is not reliable for anaerobes, *in vitro* dilution methods should be used to determine susceptibility to clindamycin.

Effective in serious aerobic gram-positive infections caused by susceptible streptococci, staphylococci, and pneumococci. The use of Cleocin PO₄ in gram-positive infections has been investigated both clinically and bacteriologically. Since it is a parenteral antibiotic, Cleocin PO₄ has been evaluated in serious infections. Its use in these infections should be reserved for penicillin-allergic patients for whom, in the judgment of the physician, a penicillin is inappropriate.

Indications include: serious lower respiratory-tract infections such as pneumonia caused by susceptible staphylococci; serious soft-tissue infections such as deep abscesses and deep traumatic or surgical wound infections caused by susceptible staphylococci and streptococci; septicemia caused by susceptible staphylococci and streptococci; and acute hematogenous osteomyelitis caused by susceptible staphylococci. In many instances the evaluated cases have been secondary to massive wounds, surgery, or debilitating disease. With few exceptions, the organisms proved susceptible *in vitro* and were successfully eradicated from the clinical lesions.

Other therapeutic considerations:

1. Cleocin PO₄ is clinically effective in serious infections caused by penicillin-resistant or penicillinase-producing staphylococci. However, staphylococcal strains resistant to clindamycin have been encountered, and susceptibility testing should be performed.

2. Cleocin PO₄ is useful in patients who are sensitive to penicillin. Clindamycin does not share antigenicity with the penicillins; however, hypersensitivity reactions have been reported with clindamycin therapy. If a hypersensitivity reaction occurs, the drug should be discontinued. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Thus, Cleocin PO₄ can fill a need for both penicillin-sensitive patients and those with serious infections caused by penicillin-resistant staphylococci.

As with all antibiotics, Cleocin PO₄ should be used with caution in atopic patients. Clindamycin has demonstrated cross-antigenicity with lincomycin.

Cleocin PO₄ should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section of the brief summary on the following page.

> If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued. (See WARNING box and summary of prescribing information on following page.)

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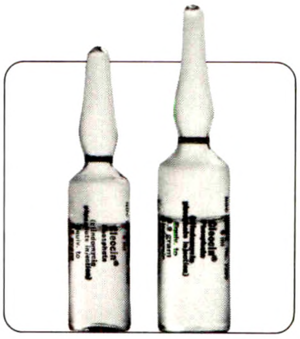
*Clostridia are more resistant than most anaerobes to clindamycin. Some species, e.g. *C. sporogenes* and *C. tertium*, are frequently resistant to clindamycin.

STERILE SOLUTION

...Cleocin® PO4

clindamycin phosphate injection, Upjohn



WARNING

Clindamycin can cause severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with the close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin base
benzyl alcohol	5 mg
disodium edetate	0.5 mg
water for injection	qs

When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (e.g., erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings:(See WARNING box.) Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro.* Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeast. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made.

Local Reactions: Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription.

For additional product information see your Upjohn representative.

MED B-4-S (NFM-3) J-4916-9

STERILE SOLUTION

Cleocin PO4

clindamycin phosphate injection, Upjohn

FOR INTRAVENOUS AND INTRAMUSCULAR USE

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001

Joint treatment against staph*:

Injection and tablets

Unipen®

(sodium nafcillin)

AS THE MONOHYDRATE, BUFFERED, WYETH

Postoperative surgical infections
Recent advances in surgical technique have been so remarkable that now total joints can be replaced with prosthetic devices. But the introduction of foreign materials—protheses, pins, nails, screws—designed to replace damaged parts or facilitate healing, can often lead to infection. Commonly, the implicated organism will be a penicillinase-producing staph. Progression can be swift and devastating.

Initial antistaph therapy: injection
It's vitally important that effective treatment of bacterial invasion begin as soon as possible. If you suspect the presence of penicillinase-producing staph and must begin therapy before definitive culture results are known, Injection Unipen® (sodium nafcillin)† is a particularly suitable agent.

Appropriate specimens for bacteriologic studies to determine the causative organisms and their susceptibility to nafcillin should be taken prior to the first dose of antibiotic.

Rapid penetration
Unipen® appears rapidly in plasma following intramuscular administration. Penetrates body tissues in high concentration and diffuses well into pleural, pericardial and synovial fluids.

"On call" capability
Reconstitutes in less than 60 seconds. Remains stable for 24 hours.‡

Follow-up therapy: tablets
Unipen is available in tablet form as well as parenteral. So the injectable form can be used initially in severe infections. And as soon as the clinical condition warrants, Unipen tablets allow you to continue antistaph therapy with the same antibiotic in a form more agreeable to most patients.

*Nafcillin-susceptible penicillinase-producing staphylococci.
†See Important Note on next page.
‡See important information under Parenteral Administration on next page.

Wyeth Laboratories · Philadelphia, Pa. 19101

See important information on next page.

Affords a specific approach to susceptible penicillinase-producing staph infections.

Unipen®

(sodium nafcillin)

AS THE MONOHYDRATE, BUFFERED, WYETH

Ease of reconstitution plus 24-hour stability in I.V. solutions put this potent antistaph agent "on call."
No precipitation, less than 10% loss in activity in I.V. solutions held at room temperature for 24 hours.†

- **5% dextrose in water**
- **5% dextrose in 0.4% NaCl solution**
- **Isotonic NaCl**
- **Ringer's solution**
- **M/6 sodium lactate solution (conc. of 30 mg/ml)**

†See "Intravenous Route" section of Brief Summary on this page.

Indications

The principal indication for sodium nafcillin is in the treatment of infections known to be due to penicillinase-producing staphylococci which have been shown to be sensitive to it.

Bacteriologic studies to determine the causative organisms and their sensitivity to sodium nafcillin should be performed.

If antibiotic therapy is considered necessary in potentially serious infections while awaiting reports of cultures and sensitivity studies, sodium nafcillin may be used to initiate therapy in such patients in whom a penicillinase-producing staphylococcus is suspected (see Important Note below).

In serious, life-threatening infections, oral preparations of the penicillinase-resistant penicillins should not be relied on for initial therapy.

Important Note

When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of sodium nafcillin should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to sodium nafcillin, the physician is advised to continue therapy with a drug other than sodium nafcillin or any other penicillinase-resistant semi-synthetic penicillin.

Methicillin is a compound that acts through a mechanism similar to that of sodium nafcillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in in vitro sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

Routine methods of antibiotic sensitivity testing may fail to detect strains of organisms resistant to the penicillinase-resistant penicillins. For this reason, the use of large inocula and 48-hour incubation periods may be needed to obtain accurate sensitivity studies with these antibiotics.

Contraindications

A history of allergic reaction to any of the penicillins is a contraindication.

Warnings

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to pencillins, cephalosporins, and other allergens. If an allergic reaction occurs, appropriate therapy should be instituted, and discontinuation of nafcillin therapy considered. The usual agents (antihistamines, pressor amines, corticosteroids) should be readily available.

Precautions

As with any potent drug, periodic assessment of organ system function, including renal, hepatic and hematopoietic, should be made during prolonged therapy.

The possibility of bacterial and fungal overgrowth should be kept in mind during long-term therapy. If overgrowth of resistant organisms occurs, appropriate measures should be taken.

The oral route of administration should not be relied upon in patients with severe illness, or with nausea, vomiting, gastric dilatation, cardiospasm or intestinal hypermotility.

Safety for use in pregnancy has not been established.

Particular care should be taken with intravenous administration because of the possiblity of thrombophlebitis.

Adverse Reactions

Reactions to sodium nafcillin have been infrequent and mild in nature. As with other penicillins, the possibility of an anaphylactic reaction or serum sickness-like reactions should be considered. A careful history should be taken. Patients with histories of hay fever, asthma, urticaria, or previous sensitivity to penicillin are more likely to react adversely.

The few reactions associated with the intramuscular use of sodium nafcillin have been skin rash, pruritus, and possible drug fever. As with other penicillins, reactions from oral use of the drug have included nausea, vomiting, diarrhea, urticaria, and pruritus.

Parenteral Administration

It is recommended that parenteral therapy be used initially in severe infections. The patient should be placed on oral therapy with this product as soon as the clinical condition warrants. **†Intravenous Route:** If given by intravenous infusion, use only these solutions—isotonic NaCl, 5% dextrose in water, 5% dextrose in 0.4% NaCl solution, Ringer's solution or M/6 sodium lactate solution (conc. of 30 mg./ml.). Discard any unused portions of I.V. solutions after 24 hours. The concentration of the antibiotic should fall within the range of 2 to 30 mg./ml. The drug concentrate and the rate and volume of the infusion should be adjusted so that the total dose of nafcillin is administered before the drug loses its stability in the solution in use.

There is no clinical experience available on the use of this agent in neonates or infants for this route of administration.

This route of administration should be used for relatively short-term therapy (24-48 hours) because of the occasional occurrence of thrombophlebitis, particularly in elderly patients.

Intramuscular route: After reconstitution, keep under refrigeration and use within 48 hours. The clear solution should be administered by deep intragluteal injection immediately after reconstitution.

Oral Administration

Beta-hemolytic streptococcal infections should be treated for at least 10 days to prevent development of acute rheumatic fever or glomerulonephritis.

If oral therapy is inadequate, resort to parenteral sodium nafcillin.

After mixing, the oral solution must be stored in a refrigerator. Discard any unused portion after one week.

Supplied

INJECTION—Vials of 500 mg., 1 and 2 Gm. Each cc. after reconstitution contains 250 mg. nafcillin buffered with 10 mg. sodium citrate. Film-coated TABLETS—containing sodium nafcillin as the monohydrate, equivalent to 500 mg. nafcillin buffered with calcium carbonate. CAPSULES—containing sodium nafcillin, as the monohydrate, equivalent to 250 mg. nafcillin buffered with calcium carbonate. FOR ORAL SOLUTION—Combination pkg. of vial of dry sodium nafcillin as monohydrate and bottle of diluent—provides 80 cc. of solution containing equivalent of 250 mg. nafcillin per 5 cc. Alcohol 2%.

WYETH LABORATORIES PHILADELPHIA, PA.

Civilian Arterial Injuries

PRAFULL V. BOLE, M.D., RICHARD T. PURDY, M.D., RINO T. MUNDA, M.D., SHA MOALLEM, M.D.,
JEGADEES DEVANESAN, M.D., ROY H. CLAUSS, M.D.

From the Department of Surgery,
New York Medical College,
New York, New York 10029

During 1968–1973, 122 patients with 126 arterial injuries were treated. In 94 instances (90 patients), these injuries involved extremities. Systolic blood pressure was below 90 mm Hg upon admission in 55.6% of all patients and 37.7% of those with injuries to arteries of the extremities. The decision for operative exploration and repair of arteries of extremities was based largely on clinical grounds (shock, loss of pulse). Preoperative arteriography was needed infrequently, while operative angiography was nearly routine. Although several cases of late revascularization or traumatic thrombosis of renal artery have been reported, hypertension complicates the postoperative period, and early, aggressive approach is essential. Mortality was 10.6%, from aortic injuries. There were no deaths among patients with arterial injuries distal to inguinal ligament or thoracic outlet. The amputation rate from reconstruction failure was 1.1%, none occurring in the last 3 years of the series. The high patency rate and lack of evidence of pulmonary embolization suggest that associated venous injuries be repaired routinely. Arterial injuries represent ideal lesions (normal arterial wall with excellent run-in and run-off). Prompt treatment of shock and early, proper management of patients' mechanical disruptions will salvage many lives and most limbs.

THIS REPORT is based on the study of 122 patients with 126 arterial injuries who were treated in this institution between January 1, 1968, and December 31, 1973. Twenty-eight patients were treated during 1968 and 1969 on the General Surgery Service. Since 1970, the Vascular Surgery Section has been primarily responsible for initial evaluation and definitive treatment of 94 subsequent cases. The ages of the patients ranged from three to 62 years, with most patients in the third decade. Twenty-two patients (18%) were female.

Distribution and Types

One hundred nine patients suffered 113 injuries to major arteries, and 13 patients had injuries to minor arteries (radial, ulnar, tibial) (Fig. 1). Ninety-four of the injuries (74.6%) affected arteries of the extremities.

In 105 instances (83.3%), the arterial injury was caused by penetration (Table 1). Sixty-three (60%) of these injuries were due to gunshot wounds, and 42 (40%) to stab wounds. Perforation, transection, or lateral laceration were the mechanisms and findings in patients with penetrating injuries.

Twenty-one injuries (16.7%) were caused by blunt trauma. Five of 12 popliteal artery injuries were nonpenetrating, due to automobile accidents or to falls from high places. In the blunt trauma group, intimal disruption, retraction, and thrombois were usual findings (Fig. 2), although transection of artery was seen also.

Acute arterial fistulae occurred in two patients (1.6%) (deep femoral and superior mesenteric arteries), both being second arterial injuries not recognized at the time of repair of major nearby vessels. False aneurysms occurred in three patients (2.4%) (brachial, 2, and external iliac artery, 1). Arterial injury was not suspected in the former two, and operation was not performed early after injury. Iliac artery trauma was missed at the time of abdominal exploration in the third patient.

Clinical Findings

Sixty-eight patients (55.6%) were admitted with hypovolemic shock. All but one patient with aortic injury (89%) were in severe shock. Shock due to major arterial injury in the abdomen or thorax persisted because continued hemorrhage exceeded the rate of replacement with Ringer's lactate solution and unmatched O negative blood infusion. Hemorrhagic shock in patients with injury distal to the inguinal ligament or thoracic outlet responded to rapid infusion of Ringer's lactate solu-

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Submitted for publication June 23, 1975.

Reprint requests: Dr. Roy H. Clauss, Professor of Surgery, New York Medical College, Fifth Avenue at 106th Street, New York, New York 10029.

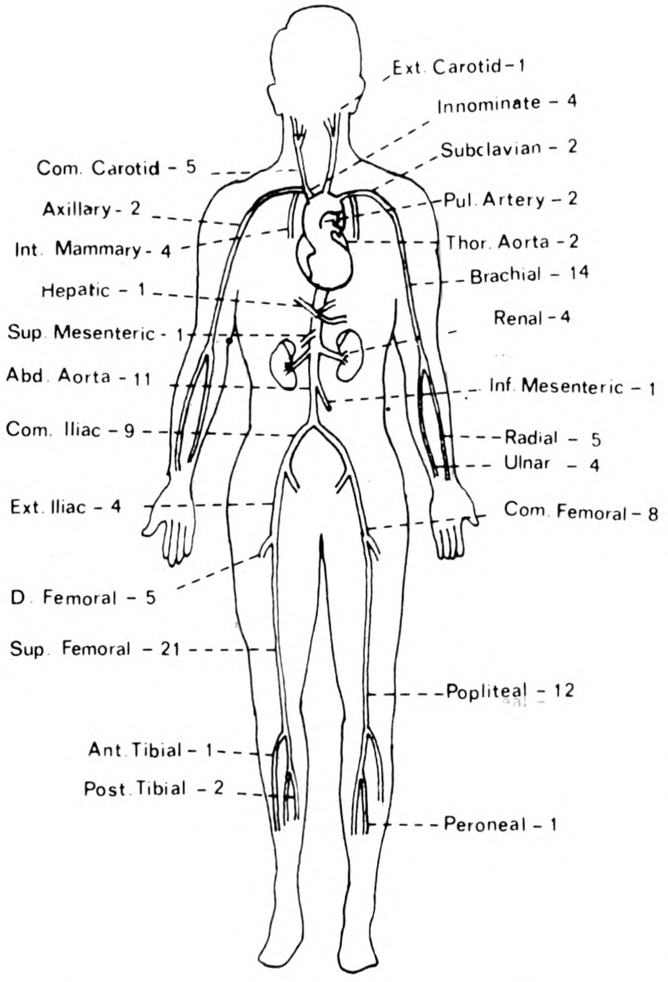

FIG. 1. Distribution of 126 arterial injuries in 122 patients.

TABLE 1. *Type of Injuries (126 Injuries)*

Mechanism	Number	%
Penetrating	105	83.3
Gunshot	63	60
Stab and puncture	42	40
Blunt	21	16.7

tion while blood was being typed and cross-matched. Thirty-four patients (37.7%) with injuries to arteries of the extremities arrived in shock.

Sixty-two of 90 patients with arterial injuries to extremities had persistent absence of pulses distal to the site of injury (Table 2). The majority of them had clinical evidence of ischemia of varying degree (paresthesias and numbness) and cold, pale, cyanotic feet. Ischemic signs were marked in 9 of 12 cases of trauma to the popliteal artery. In 20 patients, the pulses distal to injury were palpable. Expanding hematoma (10) active pulsatile bleeding (5), and bruit (1) indicated arterial injury in 16 cases. Four had injury to profunda femoris artery. In 8 patients with persistent shock, the distal pulses could not be evaluated.

Five patients had injury to the common carotid artery. Three remained in shock until operative exploration controlled causes of persistent hemorrhage. Their neurological status could not be evaluated preoperatively. The other two manifested no clinical evidence of neurological abnormality. An additional patient with injury at the origin of the left external carotid artery had contralateral hemiparesis. Persistent shock, continuous rapid bloody drainage from chest tubes, and x-ray evidence of expanding mass in the superior mediastinum indicated major vascular disruption in the intrathoracic vessels.

Abdominal major arterial injuries due to stab wounds were accompanied by shock or signs of peritoneal irritation. Clinically, involvement of various intra- and retroperitoneal arteries could not be differentiated, with the exception of renal artery trauma, which was accompanied by hematuria. Associated visceral injuries were suspected in all cases of penetrating injury to the abdomen or thorax and were identified and treated or the absence of injury verified at the time of exploration. All gunshot wounds of the abdomen are routinely explored at this institution.

Fractures in association with arterial trauma in the extremities were obvious clinically. Ischemia precluded satisfactory neurological evaluation in patients with arterial injury to the extremities. Operative exploration and postreconstruction assessment were more reliable methods of determining nerve injury or its absence.

Management

Initial evaluation of patients and injuries was performed in the Emergency Room. Patients arriving with abdominal or thoracic injury and severe shock were transfused with type O negative unmatched blood. After

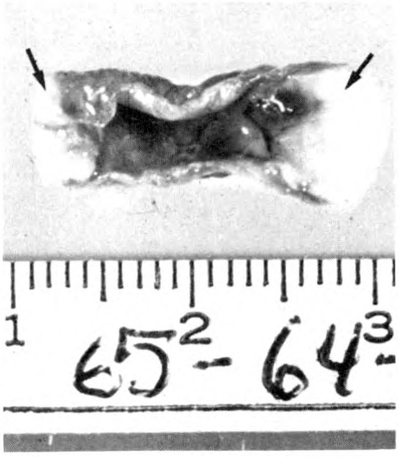

FIG. 2. Typical effect of blunt trauma upon artery—disruption and retraction of intima and media (arrows), resulting in thrombosis.

introduction of large-bore venous cannulae, central venous catheters, Foley catheter, and endotracheal tube, their wounds were explored in the operating room of the Emergency Ward. Routine intraoperative monitoring included central venous oxygen saturation measurements. Patients with arterial injuries to extremities who arrived in shock (37%, v.s.) responded to resuscitation by rapid infusion of Ringer's lactate solution. They, as were patients who were stable upon admission, were evaluated (pulses, neural function), investigated (x-ray, abdominal tap), given minor treatments (paracentesis, chest tube), and operated upon in the general operating rooms.

Preoperative Arteriography. Fifteen patients had preoperative arteriography. These included 12 patients with arterial injuries to extremities, two patients with renal artery thrombosis due to blunt trauma, and one patient with gunshot injury to the external carotid artery.

Routine preoperative arteriography has not been performed in the last 3 years. However, penetrating injury in the vicinity of a major artery in the extremity, without clinical evidence of arterial injury, was considered an indication to perform arteriography to substantiate the clinical impression and to preclude overlooking injury. Furthermore, preoperative arteriography was extremely useful when there were clinical reasons for suspecting complications of injury, aiding detection and timely and appropriate management of arteriovenous fistula, pseudoaneurysm, and causes of hemiparesis. The angiogram added no information in patients with clinically obvious injury, but only delayed arterial repair. Seven of 11 patients had isolated complete occlusion at the level of the injury (Fig. 3), and no additional information regarding the distal arterial system was obtained due to nonvisualization.

Patients with isolated extremity fracture and absent distal pulses were studied arteriographically, after reduction of the fracture, whenever feasible, even though pulses had returned. If pulses did not return, arterial trauma was presumed to have occurred. Angiograms were made in the operating room in patients with multiple fractures and suspicion of arterial injury to determine sites and effects of trauma post-reduction, unless shock required immediate intervention for associated injuries. Renal arteriography remains the only confirmatory test in patients with traumatic renal artery thrombosis because the clinical picture and pyelographic information often are ambiguous (Figs. 4 a and b).

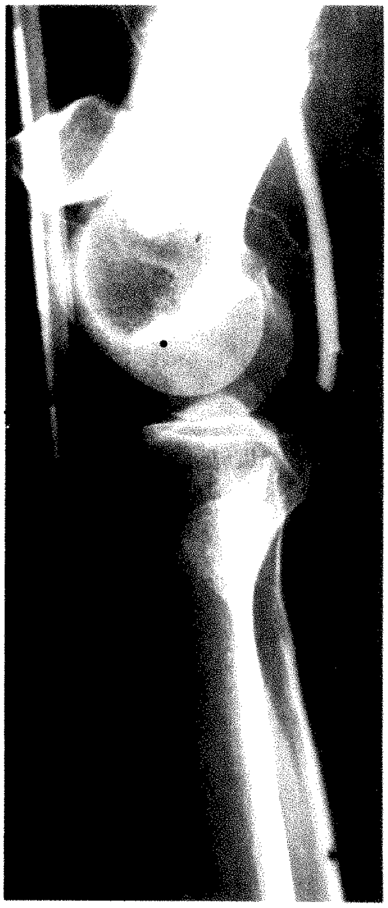

FIG. 3. Preoperative arteriogram of injured extremity without distal pulses. Angiograms are not made routinely in clinically obvious arterial injuries of extremities, for they add little information while delaying operative repair.

TABLE 2. *Clinical Presentations in 90 Patients with Arterial Injuries to Extremities*

Physical Findings	Number	%
Distal Pulse		
Absent unilaterally	59*	65.5
Present	20†	22.2
Unable to evaluate because of shock	11	12.2
Hypovolemic shock	34	37.7
Expanding Hematoma	18	20.0
External Bleeding	10	11.1
Bruit	4	4.4

* Four patients regained pulses prior to repair.

† Includes four patients with injuries to profunda femoris artery.

Intervals Between Injury and Definitive Treatment. Patients with aortic injuries were treated in the operating room of the Emergency Ward, and the interval between admission and operation was less than 20 minutes in all instances. Operative management of injuries to arteries of the neck was initiated in less than one hour, while an average of 2½ hours elapsed before operation was performed for injuries to arteries of the extremities. The longest interval (72 hours) occurred in a patient with renal artery injury due to blunt trauma, the delay caused by misinterpretation of signs and x-ray findings.

Indications for Operation. Persistent shock, rapid, unrelenting drainage of bloody fluid through thoracotomy tubes, and expanding superior mediastinal shadow on chest x-ray indicated major thoracic vascular injury. Persistent shock and return of bloody fluid upon ab-

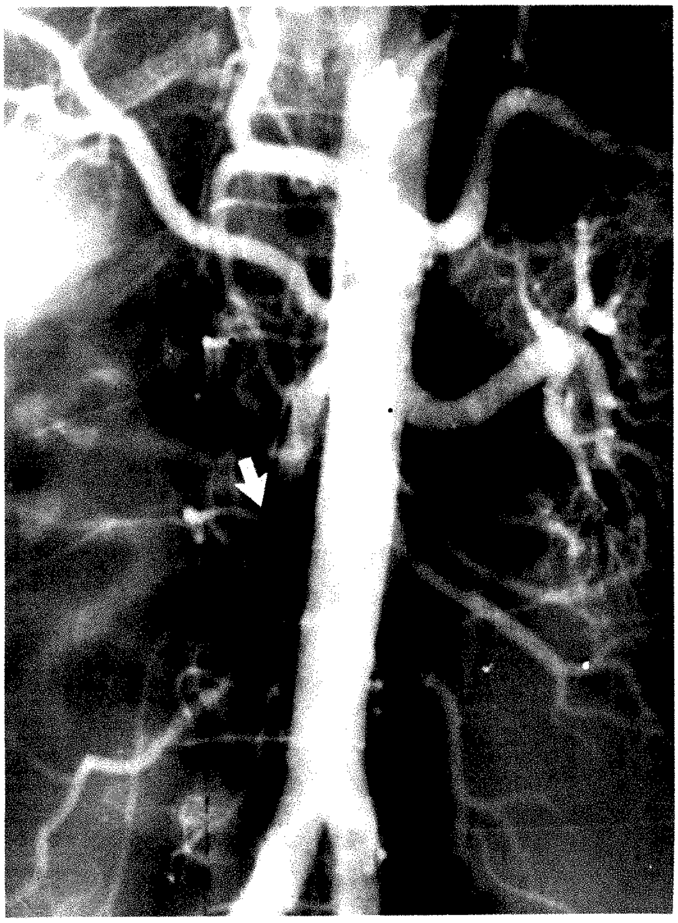

FIG. 4a. Aortogram shows tapering and occlusion of right renal artery after blunt trauma (arrow). Reconstruction was performed 72 hours after injury.

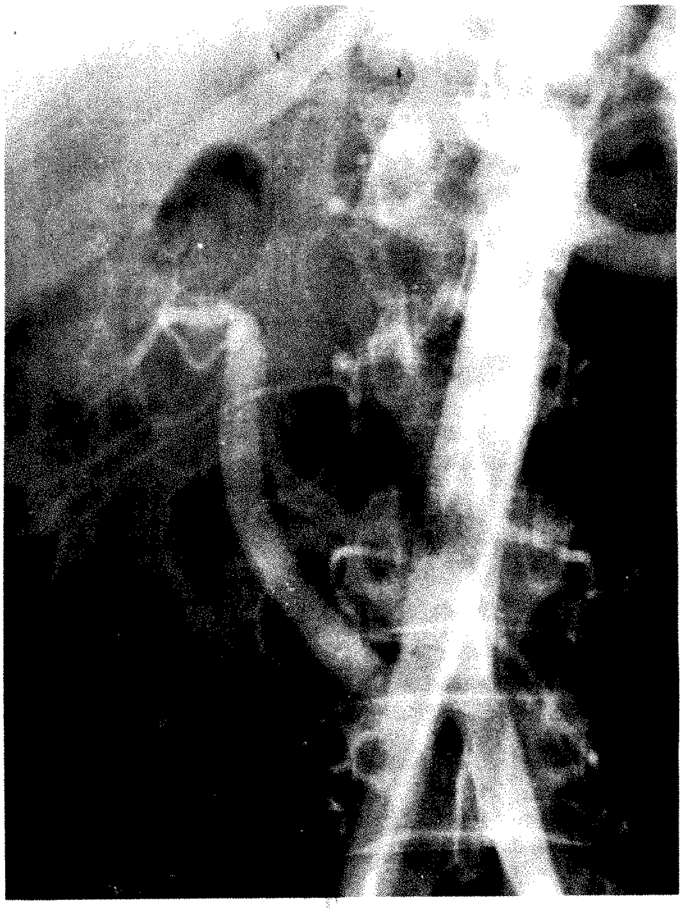

FIG. 4b. Postoperative arteriogram three weeks after surgery, showing patent Dacron graft between right common iliac artery and renal artery.

dominal tap were interpreted as abdominal vascular trauma requiring exploration. Renal artery thrombosis secondary to blunt trauma was suspected clinically and confirmed by intravenous pyelography and renal arteriography.

The indications for operative exploration of arteries of the extremities (Table 3) were transient or persistent loss of pulse, with or without evidence of ischemia, presence of large or expanding hematoma, active arterial bleeding and bruits in the area of injury. These signs were present alone or in combination. Injuries in the vicinity of major arteries were not explored in the absence of these findings; arteriography was performed instead. Patients with normal arteriograms were followed in the vascular ward and scrutinized for the development of complications of missed arterial injury. In patients with isolated fracture and absent distal pulses, the fracture was reduced and, upon return of pulse, the arterial integrity was confirmed by angiography. Patients with failure of return of pulse were subjected to operation.

Procedures (Table 4). There were 113 operations upon major arterial injuries, and repair was possible in 102

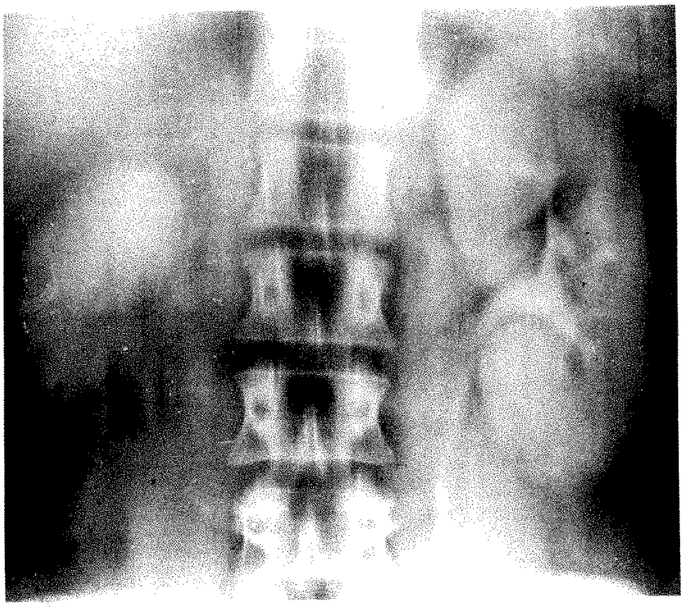

FIG. 4c. Intravenous tomo-pyelogram six months after revascularization, showing function in the right kidney five minutes after injection of contrast medium.

cases (90.2%). Thirty-two arteries were repaired simply by sutures at the site of injury. Fifty-six arteries were reconstructed by end-to-end anastomosis, with minimal resection (stab wounds with complete transection or partial transection with frayed margin, or intimal damage beyond the laceration) and, upon indication, by resection of at least one centimeter of the artery on each side of the injury (gunshot wounds and blunt trauma). Fourteen patients were treated by resection and graft replacement. Reversed autogenous saphenous vein grafting was used in 13 patients: common carotid (2), common femoral (8), popliteal (2), and brachial (1) arteries were reconstructed in this manner. In one patient with blunt trauma, a Dacron graft was placed from the right common iliac to the right renal artery. Arteries were ligated in nine patients: external carotid (1), common carotid (1), internal mammary (4), common hepatic (1), inferior mesenteric (1), and profunda femoris (1) arteries. An additional patient had ligation of the superficial femoral artery because associated massive injuries to bone and muscle were considered beyond restoration of a functional limb, and above-knee amputation was performed initially. Five of 13 minor arteries had end-to-end anastomosis; 8 were ligated. One patient with traumatic renal artery thrombosis refused treatment. Patch angioplasty was never used.

Clean, small lacerations in an artery can be managed easily with lateral repair. Irregularities or narrowing in the lumen were considered indications for resection and reconstruction to prevent turbulent or impeded flow. Frayed margins, intimal detachment beyond the lacerations, and evidence of intimal damage to the opposite wall were repaired by resection and end-to-end anastomosis. Patients with gunshot wounds required wider resections. Following resection, both ends were gently dilated, either by stripping some adventitial fibers near the edges or by using Fogarty balloon catheters, allowing end-to-end anastomosis without constriction (Figs. 5 and 6). There is reservation about the practice of routinely passing a Fogarty catheter distally to ensure absence of clots, which were found and removed in 8% of the cases. All of the distal clots were present in patients with absent pulses, and were found close to the level of the injury. If repair had been delayed, it is presumed there would have been more extensive clotting distally. Arterial anastomosis was performed, using two everting mattress sutures 180° apart, to raise a cuff to facilitate rapid, accurate placement of continuous sutures. Grafts were reserved for cases in which end-to-end anastomosis could not be done without excessive tension on the suture line despite extensive freeing of the arterial stumps proximally and distally. Vascular reconstruction is performed prior to immobilization of fractures. We prefer external fixation; occasionally internal stabilization is required.

TABLE 3. *Indications for Operations in 90 Patients with Arterial Injuries to Extremities*

Indications	Number	%
Absent Distal Pulse		
Persistent*	55	61.1
Transient	4	4.4
Expanding Hematoma Only	13	14.4
Persistent Hypovolemic Shock	11	12.2
External Bleeding Only	6	6.6
Bruit Only	1	1.1
Total	•90	

* With or without other signs.

Operative Angiography. Operative angiography is recommended following all reconstructions to detect technical errors and preclude early failures. It was particularly useful to differentiate arterial spasm (Fig. 7) from distal thrombosis when pedal pulsations were not restored after completion of the reconstruction. Angiography confirms the presence (Fig. 8) or absence of more distal thrombi and obviates potential complications of blind, repeated and unnecessary invasions of artery with a balloon catheter. Angiography detects or insures the absence of additional distal arterial injury in patients.

Fasciotomy was performed in three limbs in which extreme edema had developed after blunt popliteal trauma, with undistinguished results.

In patients with injury to the common carotid artery, monitoring of internal carotid stump pressure or ipsilateral sinus oxygen saturation or both were done in two patients. In one the stump pressure was inadequate (less than 50 mm Hg, with a systolic pressure of 150 mm Hg), and an internal shunt was used. Two patients remained in shock, one from persistent local external hemorrhage, and one due to intraabdominal hemorrhage secondary to massive injury to liver and inferior vena cava. In both patients, common carotid arteries were reconstructed without monitoring or shunts. Early in the series (1968), one common carotid artery was ligated without monitoring. An external carotid artery was ligated after extraction of thrombus from the common carotid bifurcation.

TABLE 4. *Types of Repairs (126 Injuries)*

Techniques	Number	%
Major Arteries	113	89.7
Lateral Repair	32	28.2
Resection with		
End-to-end anastomosis	56	49.5
Saphenous vein graft	13	11.5
Dacron graft	1	0.8
Ligation	10	8.0
None (refused treatment)	1	0.8
Minor Arteries	13	10.3
End-to-end anastomosis	5	38.4
Ligation	8	61.6

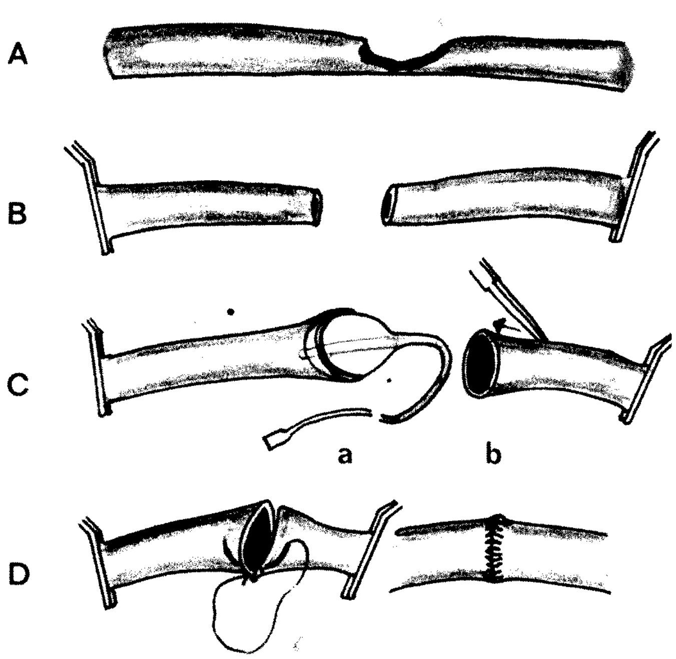

FIG. 5. a to d., (a) Loss of substance of artery. (b). Post-traumatic spasm of artery. (c) Restoration of normal caliber of lumen with intraluminal dilation or mechanical stripping of adventitia. (d). Continuous suture reconstruction with monofilament material.

Associated Injuries (Table 5)

There were 85 associated injuries. Their distribution is shown in Table 5. Ten patients with arterial injury to extremities had associated abdominal trauma requiring exploratory laparotomy for splenectomy (4) or repair of injuries to the jejunum (2), colon (3), and urinary bladder (1).

Associated venous injuries were identified in 28 patients. All 6 inferior vena cava injuries were repaired by lateral suture. Fifteen injuries in large veins of the extremities were repaired by lateral suture (7), end-to-end anastomosis (6), or short autogenous vein grafts (2).

Nerve damage was recorded in 10 instances (8.1%), but was repaired initially in only one patient with transection of the median nerve. Three of 9 nonextremity nerve injuries were managed by end-to-end or lateral repair, and no attempt at repair was made in 6 patients.

Results (Tables 6 and 7)

Among 122 patients with arterial injuries, 13 patients died, a mortality rate of 10.6%. Eight of 14 patients with aortic injuries died (53.8%). Five deaths were considered the result of associated massive abdominal injuries, even though these patients' arterial trauma had occurred in large, important arteries (common carotid (1), iliac (2), hepatic (1), and innominate arteries). No deaths occurred among patients with arterial injuries beyond the inguinal ligaments or thoracic outlet.

There were three amputations among 90 patients with 94 arterial injuries to the extremities, an amputation rate of 3.3% One was secondary to thrombosis of a vein graft for gunshot wounds of superficial femoral artery. Extensive muscle and bone trauma led to above-knee amputation in a patient with repaired superficial femoral artery injury. Local and systemic sepsis caused amputation in a third patient with a patent vein graft bridging a defect of the popliteal artery in a viable (but septic) extremity. Among 12

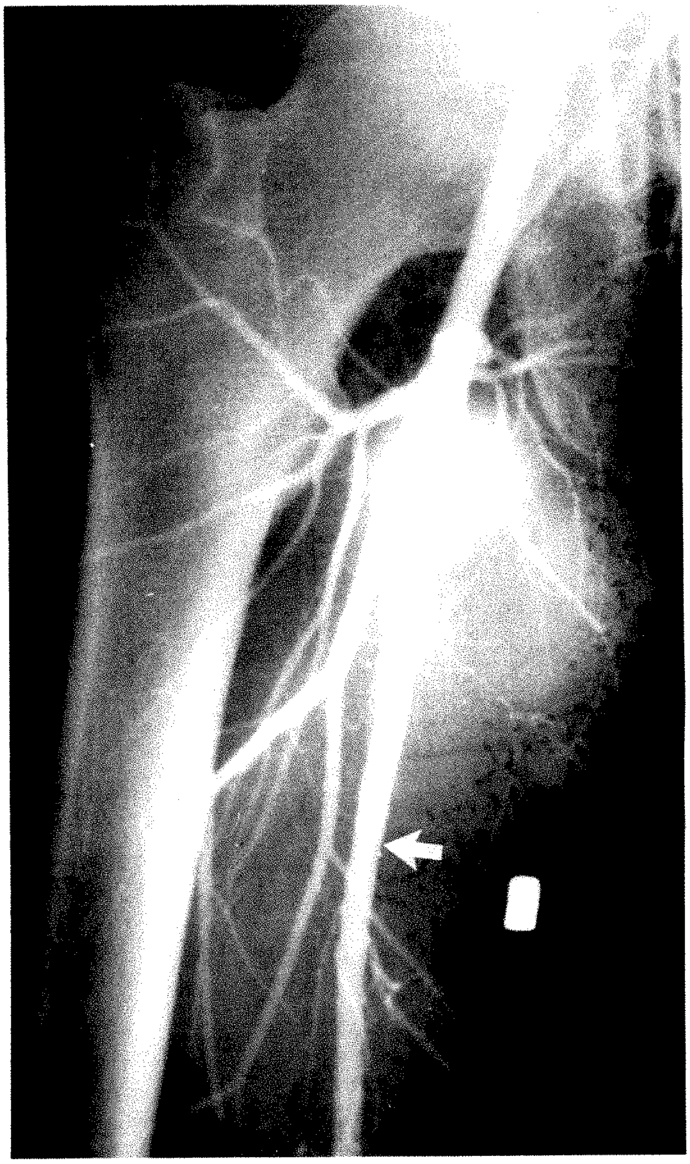

FIG. 6. Operative arteriogram showing optimal lumen resection and end-to-end anastomosis of the right superficial femoral artery. Arrow indicates the level of the anastomosis. Rectangular shadow is the retained bullet.

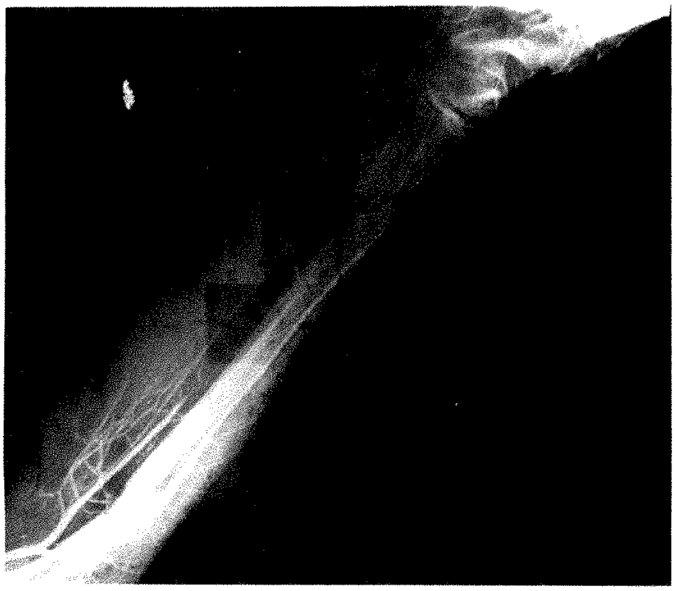

FIG. 7. Operative angiograms disclosed spasm, not intraluminal thrombus, as explanation for absent distal pulses early after operative reconstruction of traumatized blood vessel at proximal site.

patients with popliteal artery injury, only one required amputation in spite of a patent graft—a patency rate of 100% and amputation rate of 8.3%. No amputations have been necessary during the last three years of this series.

Two grafts failed. One led to amputation (v.s.). A vein graft for brachial artery trauma failed in a 7-year-old child but, because of a viable and functional extremity, no further reconstruction was attempted.

Two patients had right renal artery thrombosis due to blunt trauma. One refused surgery and has been lost to followup. The second patient's renal artery thrombosis was discovered late after pelvic fractures sustained as a pedestrian "hit-and-run" victim. A right iliac-renal artery Dacron bypass graft was performed 72 hours after admission. Two months later, postoperative arteriogram showed a patent graft, and infusion intravenous pyelogram disclosed a subnormally functioning, small right kidney (5-minute film) in a normotensive patient (Figs. 4 b and c). Peripheral vein renin concentration was normal. At 6 months, the patient developed symptomatic hypertension (190/110 mm Hg), and the right renal vein renin concentration was considerably higher than that on the left side, despite improved function by intravenous pyelography. Upon bedrest, pressure returned to normal. Peripheral renin values were normal. Right nephrectomy was performed, but the patient remains hypertensive three months after nephrectomy.

Two patients with common carotid artery transection were monitored as outlined earlier, an internal shunt being used in one patient. Both recovered without postoperative neurological deficit. Three patients were operated upon without intraoperative monitoring. One exhibited aphasia for two weeks after operation, and angiography showed nonvisualization of a branch of the ipsilateral middle cerebral artery (Fig. 9). One patient died, and death was considered due to associated massive abdominal injury. The patient treated by ligation of the common carotid had resultant hemiparesis on the contralateral side. An additional patient with external carotid injury due to gunshot wound had established hemiparesis. The cause of the hemiparesis was believed to be cerebral embolism from thrombus that was found extending from the external carotid artery into the common carotid bifurcation (Fig. 10). The patient improved subsequently and had functional extremities.

In two patients with repair of the abdominal aorta, pseudoaneurysms developed from missed posterior lacerations and were managed successfully by hypothermia and transluminal repair.

Infections at the site of injury occurred in 11 patients, mostly in extremities damaged by gunshot

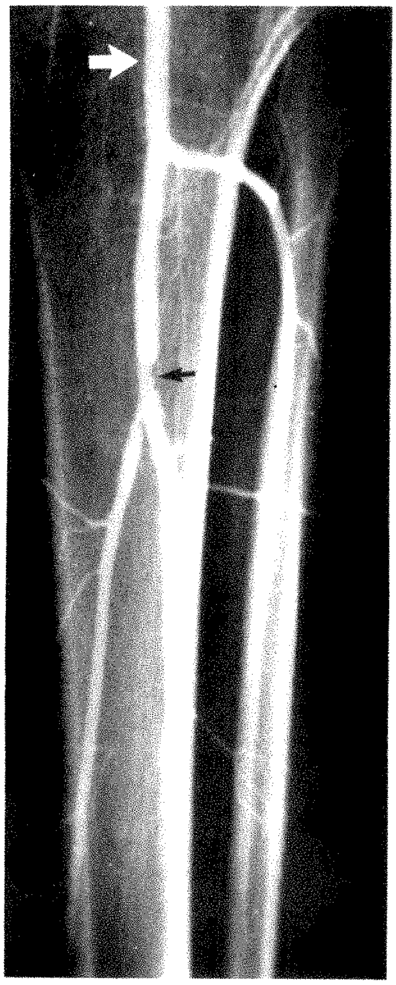

FIG. 8. Arteriogram showing retained thrombus in the tibioperoneal trunk (black arrow) after initial thrombectomy. White arrow indicates the level of the anastomosis of the popliteal artery.

TABLE 5. *Adjusted Injuries (122 Patients)*

Organ	Number	%
Veins	28	22.9
Bones	18	14.7
Nerves	10	8.1
Inferior vena cava	6	4.9
Small intestine	6	4.9
Pulmonary parenchyma	5	4.0
Liver	4	3.2
Colon	3	2.4
Stomach	2	1.6
Gall bladder	1	0.8
Urinary bladder	1	0.8
Left ventricle	1	0.8

wounds and blunt trauma. All responded to local care. No thromboses or disruptions occurred.

Postreconstruction edema was marked in popliteal artery injury (66.6%; 8 of 12 cases), despite fasciotomy in three. Edema was seen in all cases of blunt trauma to extremities with multiple fractures and crushing muscle injury. In the absence of blunt injuries, the edema was especially noticeable when arterial reconstruction was delayed and ischemic signs were prominent at the time of reconstruction.

TABLE 6. *Results of Injuries and Treatment (122 Patients)*

	Number	%
Mortality	13	10.6
Edema	12	9.8
Infection	11	9.0
Amputations	3*	3.3*
Hemiplegia	2†	
Hypertension	1	

* In 90 patients with extremity injuries.

† Includes one patient who presented with hemiplegia before operation.

TABLE 7. *Amputations (94 Injuries in 90 Patients)*

	Treatment		Amputations	
Artery	R	L	R	L
Iliac	13	0		
Common femoral	8	0		
Superficial femoral	20	1	1*	1†
Deep femoral	4	1		
Popliteal	12	0	1‡	
Tibials	2	2		
Innominate	4	0		
Subclavian	2	0		
Axillary	2	0		
Brachial	14§	0		
Radial and ulnar	3	6		
Total Injuries	84	10	2	1

* Failure of vein graft.

† Ligation considered judicious because of severe crushing injury to bones, muscles, and nerves.

‡ Reconstruction remained patent but required amputation because of septic shock from severe infection.

§ One vein graft failed in a 7-year-old child; extremity remained viable and functional.

Note: R denotes reconstruction; L denotes ligation of artery.

Five patients had postoperative venography showing patent venous repairs, including one with vein graft replacement of the common femoral vein. This graft showed marked narrowing at 3 weeks. Eight of the remaining 10 reconstructions remained patent by clinical evaluation and Doppler studies.

Discussion

The results of repair of acute arterial injuries have been superior to those of ligation in preserving function as well as viability. Important concepts regarding the significance of minimal time-lag, management of shock, techniques of surgery, types of arterial injury, associated injuries, and judicious use of fasciotomy have been derived from the cumulative military experiences of the Korean and Vietnam wars.[14] The application of these principles in civilian vascular trauma has brought about high success rates and diminished morbidity and mortality.[4,8,11–13] Most civilian vascular injuries are localized, but occasional extensive trauma comparable to that of military experience, as well as the involvement of the aging population, require expertise in intra- and postoperative cardiac and respiratory monitoring and management.

Penetrating injury to the heart and the aorta is associated with more than 80% immediate mortality. Consequently, few patients survive for transit to the operating room. Patients with blood pressure over 90 mm Hg at admission have favorable prognoses (69% survival) over patients with lower pressure (31% survival)! Thirteen of the 14 patients with aortic injury arrived with no recordable blood pressure. Operating facilities within the Emergency Ward made further transit unnecessary and immediate salvage of seven patients a reality. Preoperative transfemoral introduction of an intrathoracic balloon catheter has been recommended to prevent exsanguinating hemorrhage at the time of laparotomy.[3] Occasionally aortic injury becomes tamponaded because of the adjacency of the peritoneum and diaphragm. Suspicion, detection, and repair of these injuries are rewarded with higher salvage rates and prevent the occurrence of traumatic false aneurysms. Patients with injury in the vicinity of the aorta should have aortography if their wounds are not explored. Proper interpretation of the study is equally important. Most patients with aortic injury have multiple organ trauma. Conditions are suboptimal and, while associated injuries are being repaired, posterior lacerations in the aorta can be missed, resulting in false aneurysms. Two of the survivors in this series had this complication.[2]

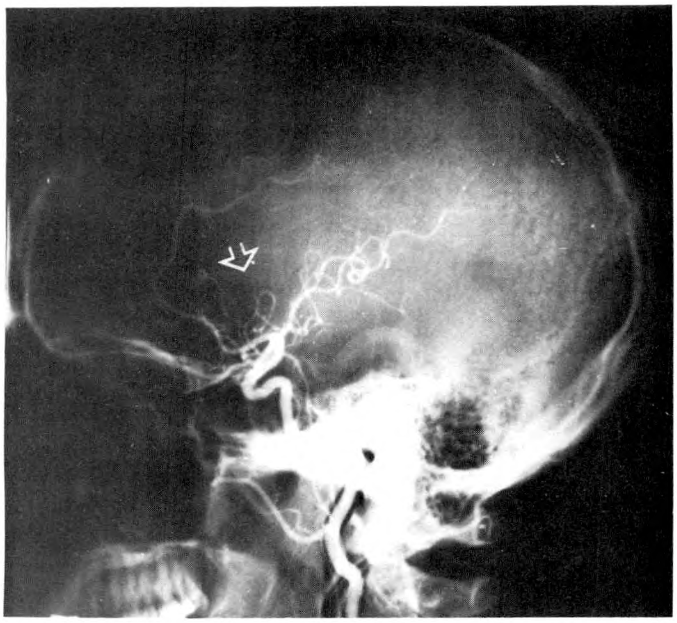

FIG. 9. Absence of visualization of branch of middle cerebral artery in patient with aphasia that disappeared two weeks after surgical reconstruction of injured common carotid artery.

Renal Artery. Most penetrating renal artery injuries are found at the time of laparotomy for trauma and can be managed by appropriate technique (lateral suture or resection with or without grafting, depending on the type and extent of the injury). Autotransplantation has been recommended when pancreatic and duodenal injuries coexist with renal artery trauma to avoid the potential complication of infection.[5] Blunt trauma is known to cause renal artery thrombosis secondary to intimal tears. Eighteen such cases have been reported, with one successful outcome not complicated by hypertension.[14] Hematuria is nonspecific and is not consistently present. Clinical suspicion, early, rapid-sequence IVP for diagnosis, and angiography for confirmation are critical factors leading to reconstruction. Failure to visualize the kidney and demonstration of occlusion of the renal artery confirm clinical suspicion. The normothermic kidney can survive up to two hours of total ischemia. However, collateral vessels may provide enough perfusion to keep the nephrons viable for days. They would be nonfunctional under these circumstances, but return of function is possible following arterial reconstruction. The presence of a nephrogram effect despite occlusion of the renal artery indicates the functional adequacy of such collateral arteries, which occasionally have been demonstrated angiographically.[9] Successful renal artery reconstruction with kidney salvage has been reported as late as 12 hours after injury. One case in this series was reconstructed 72 hours after trauma, with return of some function. The incidence of postoperative hypertension is difficult to predict, since clinical circumstances have been so varied in the few cases observed. Postoperative delayed hypertension remains a potential complication necessitating eventual nephrectomy.

Carotid Artery. The importance of adequate blood volume and hydration, of hypertension, hypercarbia, internal carotid artery stump mean pressure, and monitoring of lateral sinus oxygen saturation have been emphasized in the management of occlusive carotid lesions. These principles have been applied in trauma patients, also, with good results. Intraoperative monitoring and use of shunts become important, since the presence of shock limits blood flow from the contralateral side. Extensive carotid trauma often involves grafts, requiring cross-clamping time significantly longer than in elective carotid endarterectomy. While trauma patients are mostly in the younger age group, and the remaining extracranial circulation may be expected to be normal, it is not necessarily adapted to compensatory cross-filling. Postoperative neurological deficit may be

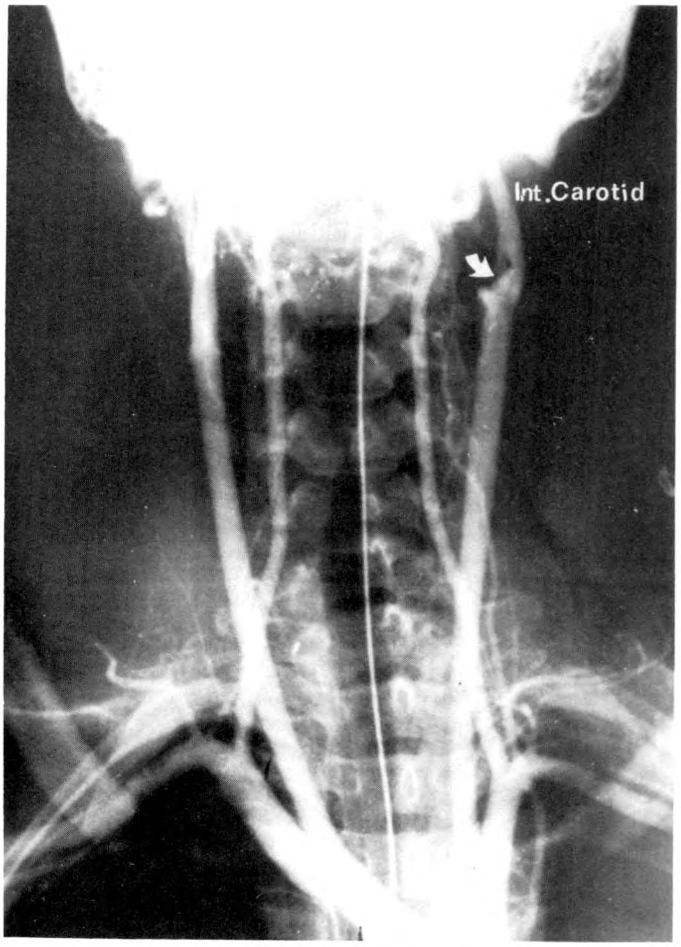

FIG. 10. Preoperative arteriogram in the patient with injury to the left external carotid artery and contralateral hemiparesis. Thrombus (arrow) extends into the internal carotid artery. (Intracranial visualization was not recorded.)

circumvented by responding to information from monitoring and the use of adjuncts and shunt as necessary. Proximal external carotid lesions can cause or contribute to the development of neurological deficit, as seen in one instance in this series.

Arterial Injury to Extremity. In most patients with trauma to the extremity, arterial injury is obvious because of ischemic signs and absent pulses. Transient loss of pulse unilaterally may be as significant as persistent loss. Four patients in this series had transient loss of pulse, and arterial injury was confirmed at exploration. Presence of pulse does not rule out arterial injury; 22.2% of our patients with confirmed arterial injury to extremities had palpable distal pulses. Large or expanding hematoma, rapid arterial bleeding, and presence of bruit were additional reliable indicators that led to clinical diagnoses of arterial trauma in these cases. Expanding hematoma may be caused by transection of a major vein (e.g., superficial femoral) or by lacerations of muscular branches of arteries.

Approximately 20 patients (not qualified for inclusion in this series) with injuries in the vicinity of major arteries in the extremities were admitted to hospital for observation. Operation was not performed because of lack of clinical findings indicating arterial trauma. Sixteen had normal angiograms and did not develop complications of missed arterial injury; four refused the study. One of these returned subsequently with arteriovenous fistula of a branch of lateral circumflex artery, treated by ligation. With this experience we have continued to limit explorations only to patients with clinical evidence of arterial injury, preferring angiography in patients with trauma close to major vessels.

Observation is recommended in one report when findings are not clear-cut (foot or hand cool rather than cold, hypesthetic rather than anesthetic, and pale rather than ashen).[11] Sympathetic block, blood transfusions, and even hyperbaric oxygenation have been recommended while delaying the decision to operate.

We have found that clinical indices are significant even when present to a slight degree. In their total absence, close observation may be undertaken. Arteriography can be obtained but is most likely to be normal. We continue to obtain angiographic confirmation of clinically ruled-out arterial injury.

Experience with ligation of arteries of the upper extremity in World War II resulted in an amputation rate that ranged from 25% to 55%, depending on the artery ligated.[8] Severe ischemic symptoms and disabilities in the upper extremity after arterial trauma have been reported in civilian injuries, and routine reconstruction is recommended.[8]

Ischemic symptoms follow ligation of the profunda femoris artery,[7] and attempts must be made routinely to reconstruct this important conduit and end artery. Recent literature has shown amply the flow capacity and contribution of this artery in chronic occlusive disease.

Occasionally associated muscular, skeletal, or neural injury is extensive, and the decision between reconstruction and primary amputation becomes difficult. We recommend initial reconstruction and debridement, with subsequent amputation if necessary. Among 4 patients with multiple injuries (fractures of femur, upper and lower tibia (3), popliteal artery transection and injury to nerves (2), crushing trauma to leg muscles (4), deeply lacerated perineum (1), and ruptured spleen requiring splenectomy (2) from falls from high places and automobile accidents), three patients subsequently were discharged with viable and functional extremities after prolonged hospital stays. One required amputation because of sepsis. In all cases, amputation was considered initially but reconstruction with debridement of damaged soft tissues, internal fixation, or skeletal traction was done.

The amputation rate after civilian arterial injury to the extremities has been reported in the proximity of 7%.[4] One series reported a lower amputation rate.[16] The over-all amputation rate in our patients was 3.3%. The lower extremities of patients in this series may have been at risk of amputation only 54 times (secondary to injuries in 13 iliac arteries, 8 common and 21 superficial femoral arteries, and 12 popliteal arteries), raising the amputation rate to 5.6%. Calculated yet another way, three amputations in 33 limbs in which superficial femoral or popliteal arteries were repaired, the percentage of amputations is 9%. However, only one of these three events followed thrombosis in a repaired vessel, reducing the presumably avoidable amputation rate to 3%, virtually the same as the overall rate, the conventional method of reporting. The amputation rate after popliteal artery trauma has been reported to be from 17%[13] to 43%.[4] In our series, it was 8.3%. No amputations have been necessary in the last three years of our experience.

Postreconstruction edema constitutes a significant problem in cases of marked ischemia and blunt trauma associated with skeletal and muscle injuries. In such cases, fasciotomy remains an open question. Some consider it an important adjuvant[13] if other conservative measures fail.

It is our policy to anticipate and to attempt to prevent edema by high elevation of the injured extremity early after trauma and treatment. The severity of edema has seemed related to injuries of popliteal space, of bone and muscle at any site, and to duration and severity of ischemia.

Edema seemed unrelated to possible loss of patency of repaired major veins. We do not perform venography in the presence of clinically obstructed veins, wary of inducing thromboses in collateral channels. Limited experience with fasciotomy and failure to prevent edema in high-risk circumstances suggest we have yet to find better modes of timing of ideal treatment to limit severe edema in susceptible circumstances.

Occlusion of venous return reduces the arterial inflow and may compromise arterial reconstruction.[6] It also contributes to the development of postoperative edema. However, ligation of a traumatized major vein is often recommended because of the possible threat of pulmonary embolism.[12] Fifteen concomitant venous injuries were repaired in this series. The patency rate has been encouraging. Routine lung scans were not done because there were no symptoms suggestive of, or deaths from, pulmonary embolism.

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Gastrointestinal Hemorrhage from Adhesion-related Mesenteric Varices

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As a result of this retrospective analysis of hemorrhage from a porta-systemic venous shunt occurring within the small intestine, we believe that the early diagnosis of the syndrome is strongly suggested by the presence of varices in unusual locations demonstrated by the venous phase of mesenteric arteriography. In all patients portal hypertension was present, and in all the affected bowel was adherent to postoperative adhesions on old suture lines. The syndrome was treated variously with lysis of adhesions, bowel resection, or portal-systemic shunt. Those patients with excellent hepatic reserve survived and had no further gastrointestinal bleeding.

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GASTROINTESTINAL TRACT HEMORRHAGE secondary to varices is a frequent complication of portal hypertension usually resulting from intrahepatic block due to hepatic cirrhosis. Bleeding most commonly occurs from portal-systemic venous shunts at the cardio-esophageal junction and occasionally from shunts around the anal canal. However, an infrequent site of gastrointestinal tract hemorrhage has been reported to be submucosal intestinal varices in the territory of the superior and inferior mesenteric veins.[5] Six cases of gastrointestinal hemorrhage from this unusual source were observed between February, 1968 and December, 1974 at the Massachusetts General Hospital. The significant feature of all of these cases was that the submucosal varices occured at sites of postoperative intra-abdominal adhesions. The following reports chronicle the presentation, clinical course and fate of each case.

Case Reports

Case 1: A. B., MGH Unit No. 196-60-29

A 71-year-old diabetic woman was transferred from another hospital on December 6, 1974 to the Massachusetts General Hospital for further evaluation of continued frank rectal bleeding after normal barium enema and upper GI series, negative sigmoidoscopy and negative gastroscopy. She had undergone abdominal hysterectomy 18 years prior to admission and had a history of azotemia presumably secondary to nephrosclerosis. Prior to admission she had been transfused 15 units of whole blood.

Physical examination revealed on icteric female with a slightly enlarged liver and a spleen palpable two fingerbreadths below the left costal margin. There was red blood in the rectal ampulla and a guaiac negative nasogastric aspirate. Entry hematocrit was 29% and WBC 3,500 with 87 PMN's, 1 band, 3 lymphs and 9 monos. Urinalysis was essentially unremarkable. Platelet count was 45,000, PT 13.6/11.9 sec and PTT 35.4. BUN was 58 mg% and blood sugar 185 mg%. Serum albumin was 3.5 gm%, bilirubin 0.5/1.0 mg%, alkaline phosphatase 2.8 Bodansky units and creatinine 2.1 mg%.

Chest film was clear, and a selective superior mesenteric arteriogram showed marked diffuse atheromatous disease with no extravasation of contrast medium into small bowel or visualized portions of colon. There was, however, a noticeable dilation of a distal portion of the superior mesenteric vein. A repeat arteriogram with a longer filming sequence demonstrated large venous structures in the region of the distal ileum and apparently in the neighborhood of the left ovarian vein. A selective celiac arteriogram showed an enlarged spleen and widely patent splenic and portal veins. Some reversal of flow was apparent in the superior mesenteric vein, and no esophageal or gastric varices were identified.

Selective hepatic venous pressures in the wedge position were 24 cm of H_2O and in the free position 7 cm of H_2O with an inferior vena caval pressure of 6 cm of H_2O. The left ovarian vein pressure was 13 cm of H_2O. The mean sinusoidal pressure of 18 cm of H_2O was felt to represent portal hypertension.

In light of the patient's severe atherosclerotic vascular disease, infusion of vasopression was thought to be hazardous. Further gastrointestinal bleeding led to exploratory laparotomy on December 12, 1974. The omentum was densely adherent to the entire area of the prevous lower abdominal incision and many vascular adhesions were taken down. She had a very nodular cirrhotic liver, and there was no marked evidence for portal hypertension in the retroperitoneum. The distal portion of the small bowel was found to be filled with blood, and distal ileum exhibited extremely dilated veins within its

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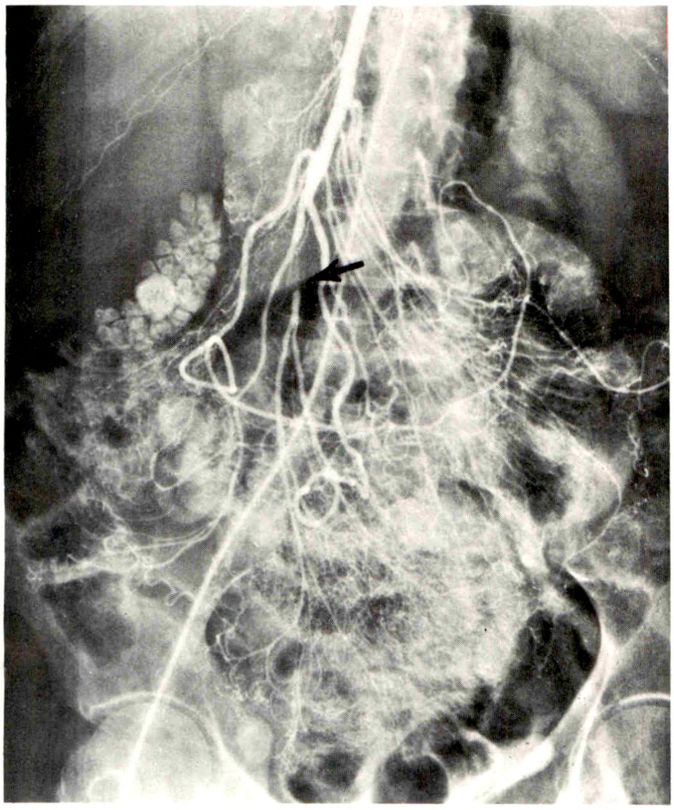

FIG. 1a. The superior mesenteric anteriogram shows diffuse atherosclerotic changes of the superior mesenteric artery with occlusion of an iliac artery (arrow). No arterial bleeding site is identified. Incidental note is made of numerous calcified gallstones in the gallbladder.

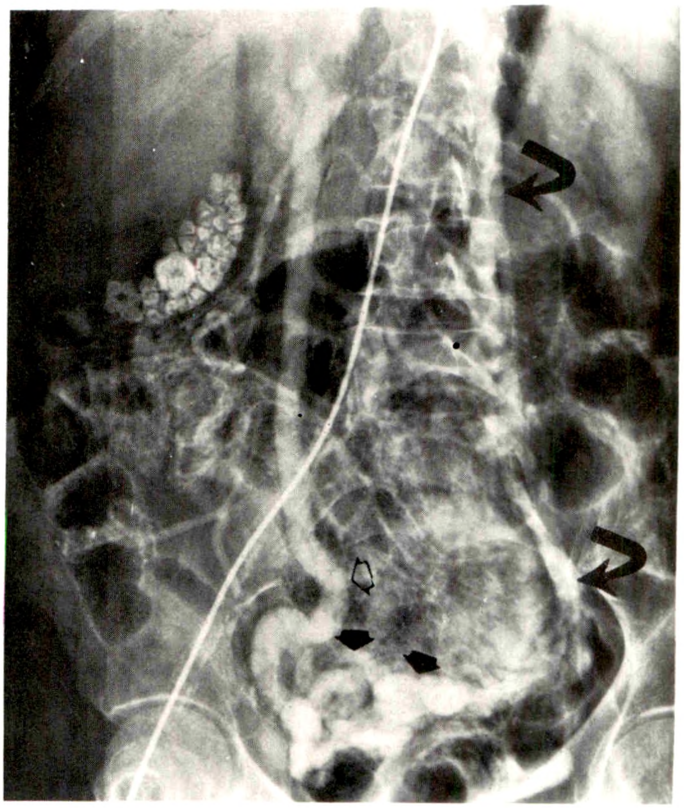

FIG. 1b. Venous phase of the superior mesenteric arteriogram demonstrates a patent superior mesenteric vein with a dilated ileal vein (open arrow) and ileal varicosities (closed arrows) draining into the left ovarian vein (curved arrow).

mesentery extending over the surface of the intestine up into an adhesion, which bound the ileum to the left pelvic wall at the site of the previous peritoneal incision for hysterectomy. A one-foot segment of ileum was resected, the very large vein doubly ligated, and a standard end-to-end small bowel anastomosis performed. Histological examination of the resected small bowel demonstrated a ruptured submucosal varix. Subsequent myocardial and renal failure could not be successfully treated, and the patient eventually died on January 17, 1975 (Figs. 1a to c).

Case 2: L. S., MGH Unit No. 121-79-35

A 38-year-old chronic alcoholic woman was admitted to the Massachusetts General Hospital on March 11, 1974 with a complaint of frank rectal bleeding of four days' duration. Significant medical history included intermittent blood staining in her stools for two years prior to admission and a salpingo-oophorectomy at the age of 20.

Physical examination revealed a hypotensive female with a liver palpable four fingerbreadths below the right costal margin. The spleen could not be palpated. Nasogastric aspirate was guaiac negative and rectal examination showed frank blood. Entry hematocrit was 18%, serum albumin 2.0 gm%, serum bilirubin 2.7/3.6 total, SGOT 37 and alkaline phosphatase 7.9 Bodansky units. Sigmoidoscopy to 25 cm showed red blood without mucosal abnormality.

Selective superior mesenteric arteriograms disclosed a normal appearing arterial anatomy with no localized arterial extravasation. A venous phase demonstrated extremely large venous structures in the pelvis. These were associated with dilated veins in the small bowel mesentery and eventually emptied into the inferior vena cava. No forward flow toward the portal vein was visualized.

An infusion of vasopressin into the superior mesenteric artery was begun, which seemed to control the bleeding. Over a period of 12 hours the infusion was lessened and 5 hours later the patient developed another episode of lower gastrointestinal bleeding. The fol-

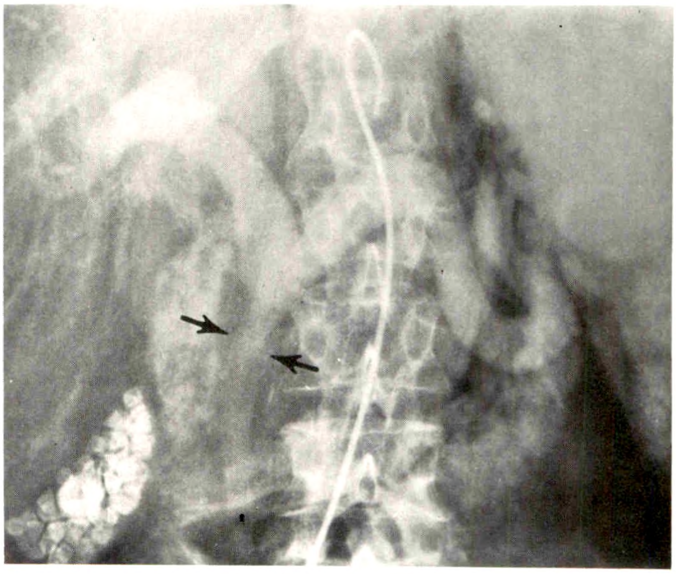

FIG. 1c. Venous phase of the celiac arteriogram demonstrates splenomegaly and patent splenic and portal veins with retrograde flow into the superior mesenteric vein (arrows). No gastric or esophageal varices are opacified.

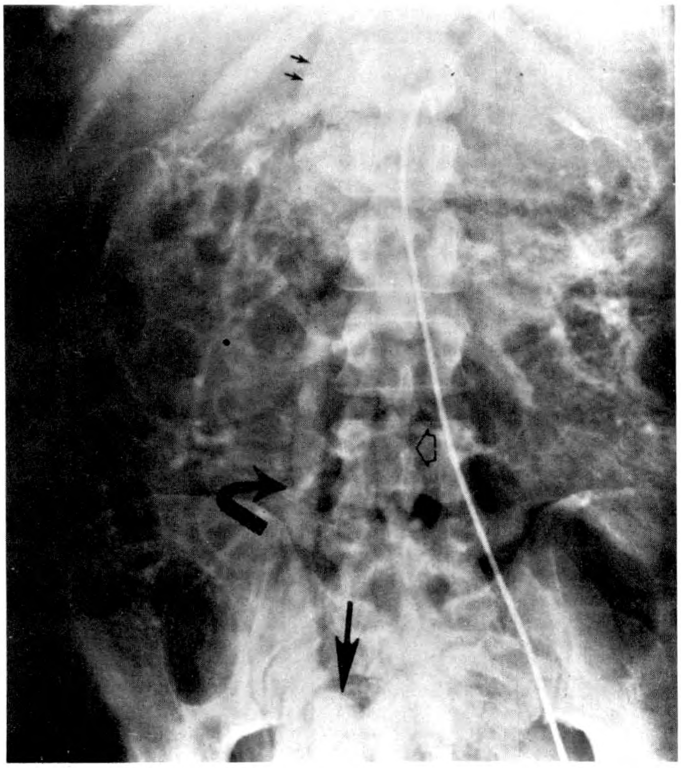

FIG. 2. The venous phase of a superior mesenteric arteriogram demonstrates patent superior mesenteric vein with a dilated ileal vein (open arrow) and varicosities (large arrow) which drain into the right ovarian vein (curved arrow). There is opacification of the suprarenal inferior vena cava (small closed arrows).

lowing day the patient's abdomen was explored, revealing a nodular, slightly enlarged liver. Massively dilated veins in the mesentery of the distal ileum communicated with enormous systemic venous structures throughout the area of the previous ovarian cystectomy. Distal ileectomy and right colectomy were performed with primary end-to-end anastomosis.

Histological examination of the resected distal ileum and proximal colon showed prominent veins in the ileal submucosa and the serosal adhesions of ileum and cecum. Mucosal denudation over an ileal varix was also noted. Subsequently, the patient developed a bleeding diathesis and renal failure, dying on March 22, 1974 (Fig. 2).

Case 3: T. M., MGH Unit No. 149-18-89

A 49-year-old alcoholic woman with a long history of cirrhosis was admitted on February 27, 1968 with rectal bleeding and hepatic encephalopathy. Prior to this admission she had undergone an abdominal exploration (19 years ago) for investigation of a right-sided abdominal mass which was found to be an enlarged liver. On that occasion an appendectomy was performed. One week prior to her admission to the Massachusetts General Hospital she had entered an outside hospital because of rectal bleeding and a hematocrit of 29%. At that time, a barium enema and upper GI series failed to reveal a definite abnormality. On admission here, the patient was found to be anicteric and stuporous and barely arousable by noxious stimuli. There was a huge mass palpable in the right abdomen that appeared to be liver. Spleen could not be felt, and there was no apparent ascites or peripheral edema. Entry hematocrit was 24%, Van den Bergh 0.9 mg%, serum albumin 3.1 gm% and alkaline phosphatase 5.1 Bodansky units. SGOT was 46. Serum NH_3 was greater than 150 mcg%.

Gastrointestinal bleeding initially quiesced, and the patient's hepatic encephalopathy gradually cleared. Subsequent workup included sigmoidoscopy and repeat barium contrast examination of upper and lower GI tracts, all of which were normal. The patient again experienced rectal bleeding and at subsequent exploratory laparotomy on March 9, 1968 was found to have minimal ascites and a cirrhotic liver with a tremendously enlarged right lobe. A loop of ileum was adherent to the previous laparotomy incision with an extremely large dilated mesenteric vein leading from it. Dense adhesions with venous communications extended from this portion of the ileum into the abdominal wall. The blood that could be seen in the intestinal tract appeared to be distal to the adherent loop of ileum. The involved segment of ileum was freed, the dilated mesenteric vein ligated and divided and the raw surface of ileum turned in with interrupted fine sutures. Before the abdomen was closed, the portal venous pressure was measured in one of the gastroepiploic veins. This was 31 cm of saline with a systemic blood pressure of 110/70. The patient's convalescence was unremarkable, and there was no recurrence of gastrointestinal bleeding.

Case 4: G. B., MGH Unit No. 182-11-25

A 63-year-old man was admitted to the Massachusetts General Hospital on November 29, 1973 with a two-week history of weakness and tarry stools.

In May, 1971 a laparotomy was performed at another hospital for obstructive jaundice. A large mass in the head of the pancreas was suggestive of pancreatic carcinoma, and a retrocolic Roux-en-Y cholecystojejunostomy was performed. No biopsy was obtained. Postoperatively, the patient was treated with 5-Fluorouracil and did well with a stable weight and relief of his jaundice. Eighteen months after his initial operation, although he was asymptomatic, he was referred to the Massachusetts General Hospital for reevaluation of the initial diagnosis. Angiography demonstrated a patent but encased portal vein and obliteration of several intrapancreatic arteries, all consistent with pancreatic carcinoma. Six months later in June, 1973 a second laparotomy was performed at the initial hospital to establish a definitive diagnosis. Pancreatic biopsy showed only fibrosis, and 5-Fluorouracil was discontinued.

From this point he began to lose weight, and after a 20-lb weight loss he again was seen at the initial hospital with gastrointestinal bleeding. Workup demonstrated a few diverticula on barium enema and a normal upper GI tract, but esophageal varices were seen on esophagogastroscopy. They were not actively bleeding and no blood was present in his stomach. After 8 units of blood replacement over 11 days, he was transferred to the Massachusetts General Hospital on November 29, 1973.

Entry hematocrit was 25%, nasogastric aspirate revealed no blood in his stomach, and his stool was tarry and 4+ guaiac. PT, PTT and platelet counts were normal. Serum bilirubin was 0.2 mg%, SGOT 10, alkaline phosphatase 7.6 Bodansky units and serum albumin 2.3 gm%.

Angiography demonstrated near total occlusion of the hepatic artery and total occlusion of the intrapancreatic portal vein at the confluence of his splenic and superior mesenteric veins. There appeared to be jejunal varices at the site of the previous cholecystojejunostomy, but no bleeding point was demonstrated.

Over the next 5 days he required 8 units of blood replacement. On December 3, 1973 a 19 mm dacron mesocaval shunt was performed. Multiple pinpoint nodules on the peritoneal surface proved to be adenocarinoma on biopsy. Large venous connections were apparent between the area of cholecystojejunostomy and the abdominal wall. Postoperatively his bleeding ceased, but he died of myocardial failure on his 26th postoperative day (Fig. 3).

Case 5: B. L. M., MGH Unit No. 151-76-27

A 16-year-old girl was admitted to the Massachusetts General hospital on July 23, 1968. She had experienced esophageal variceal hemorrhage at age 2 and at age 3 underwent a splenectomy, distal esophagectomy and proximal gastrectomy with colonic interposition. Since then she had experienced three major episodes of massive bleeding, all manifested by tarry stools without hematemesis. She was referred to the Massachusetts General Hospital for portal-systemic shunt surgery.

Physical examination revealed no signs of chronic liver disease and, except for abdominal scars, the remainder of the physical examination was unremarkable. Her entry hematocrit was 32%, serum bilirubin 0.3 mg%, alkaline phosphatase 14 Bodansky units and serum albumin 4.4 gm%.

A celiac and superior mesenteric angiogram in its venous phase disclosed extrahepatic portal vein occlusion with peri-portal collateral present and no esophageal varices. Also evident was a prominent jejunal venous trunk draining to a region of the superior mesenteric vein where multiple varicose channels fed into peri-portal collateral vents to the intrahepatic venous system.

Exploratory laparotomy on August 2, 1968 revealed a loop of jejunum with a large vein within its mesentery and vascular adhesions between it and the abdominal wall. The adhesions were severed to free the bowel, and thereafter, a saphenous vein graft was constructed between a mesenteric vein and the inferior vena cava. The patient's postoperative convalescence was unremarkable and she was discharged on August 17, 1968.

Case 6: E. C., MGH Unit No. 185-81-84

A 64-year-old woman was admitted to the Massachusetts General Hospital on July 3, 1973 with a history of gastrointestinal hemorrhage treated at another hospital in February, 1973. Workup at that time revealed the presence of esophageal varices, but no bleeding could be documented from the upper gastrointestinal tract. Total blood replacement was 7 units of whole blood, and no source of bleeding was found. One month later the patient experienced another episode of gastrointestinal hemorrhage. Nasogastric aspirate was negative for blood, contrast workup of the upper and lower GI tract was essentially negative, and a sigmoidoscopy showed a 4+ guaiac positive stool without apparent bleeding source. Colonoscopy revealed a small polyp of the splenic flexure. The patient was transfused a total of 4 units of blood.

On June 19, 1973 the patient was transferred to the Massachusetts General Hospital after a further episode of gastrointestinal hemorrhage. Entry serum bilirubin was 2.5 mg%, and serum albumin was 3.3 gm%. The remainder of the liver profile and bleeding parameters were within normal limits. Esophagoscopy showed varices which were not bleeding and gastroscopy failed to reveal lesions within the upper GI tract or blood within the stomach. An aortogram demonstrated occlusion of the superior mesenteric vein at its confluence with the splenic vein; the splenic and portal veins were patent. Portal hypertension was evidenced by retrograde opacification of the inferior mesenteric vein and umbilical vein. It was concluded that the bleeding originated in the inferior mesenteric artery distribution although no definite site was demonstrated. Hepatic artery tortuosity was also noted and interpreted as a sign of probable hepatic cirrhosis. Total blood replacement was 5 units of whole blood.

On the occasion of the present admission the patient presented with bright red rectal bleeding. Blood pressure was 160/90 and the pulse was 120 and regular. The remainder of the physical examination was within normal limits with the exception of the presence of the rectal bleeding. The admission hematocrit was 21% and liver profile showed total protein of 4.5 gm% with albumin 2.5 gm%, total bilirubin 0.5 mg% and SGOT of 31. Prothrombin time was 13.3/12.0 sec and platelet count was 69,000.

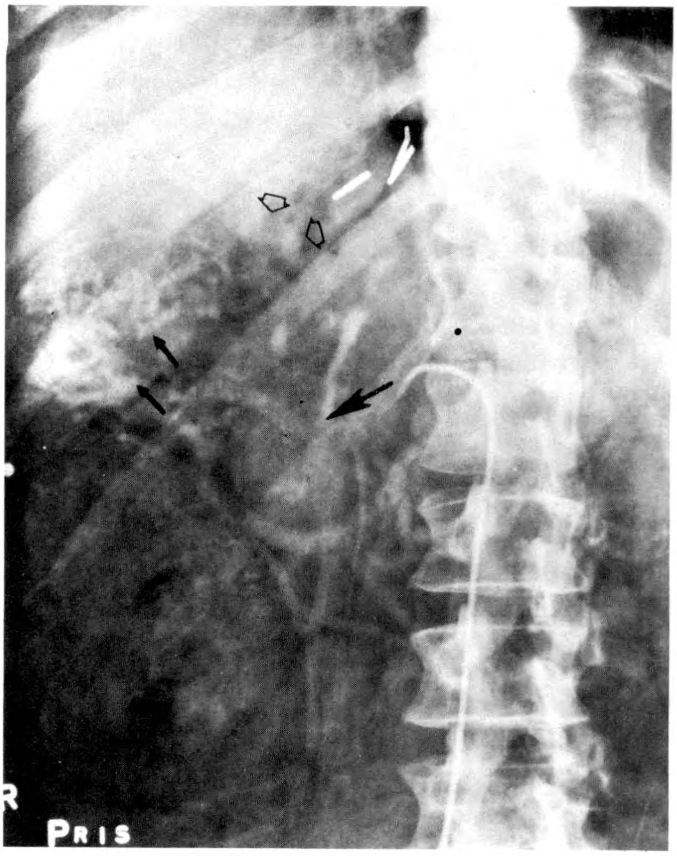

FIG. 3. Venous phase of the superior mesenteric arteriogram demonstrates occlusion of the superior mesenteric vein (large arrow) by the carcinoma of the pancreas. Large duodenal varicosities (small arrows) drain into the portal vein (open arrows) beyond the area of occlusion by the neoplasm.

Because of continued bleeding, the patient again underwent angiography. This demonstrated occlusion of the superior mesenteric vein. A large ileocolic vein was seen in the right lower quadrant and reflux through the gastroduodenal artery demonstrated irregular tortuosity of a hepatic vessels consistent with cirrhosis of the liver. Esophageal varices were also demonstrated. Infusion of vasopressin resulted in prompt cessation of the bleeding. Because of the numerous bleeding episodes, all documented as being from the lower GI tract, surgical exploration seemed indicated. Since there was angiographic evidence that the superior mesenteric vein was occluded and that the patient essentially had two separate portal systems—one including the portal and splenic veins and the other including the superior mesenteric vein which apparently drained through multiple collateral veins—it seemed that venting the superior mesenteric vein into the vena cava or adjacent iliac vein should control the hemorrhage.

At exploratory laparotomy on July 10, 1973 a two-foot segment of mid-ileum was found to be densely adherent to the overlying abdominal wall at the point of a previous appendectomy incision. Within the wall of the small bowel was a racemose venous system with very high venous pressure, and massive bleeding occurred during the dissection of the adhesions. Adjacent to a vascular portion of small bowel there was a large vein which measured 1 cm in diameter within 1 cm of the bowel wall and became progressively larger as it exited toward the base of mesentery. On either side of this vein,

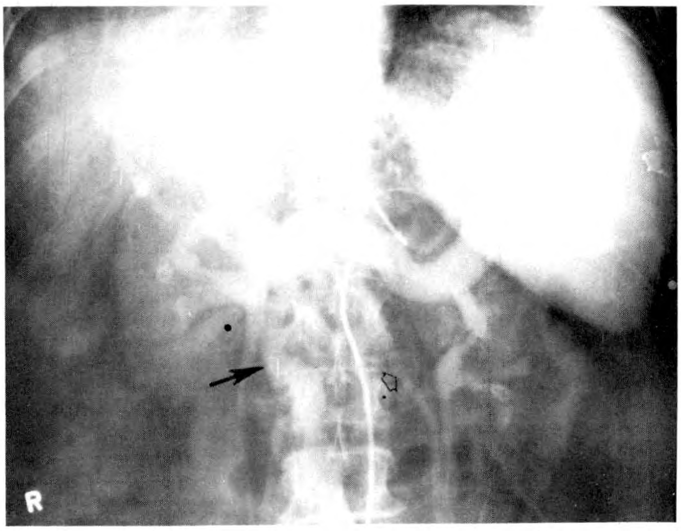

FIG. 4a. The venous phase of a celiac arteriogram demonstrates retrograde flow into the superior mesenteric vein (arrow) and the inferior mesenteric vein (open arrow).

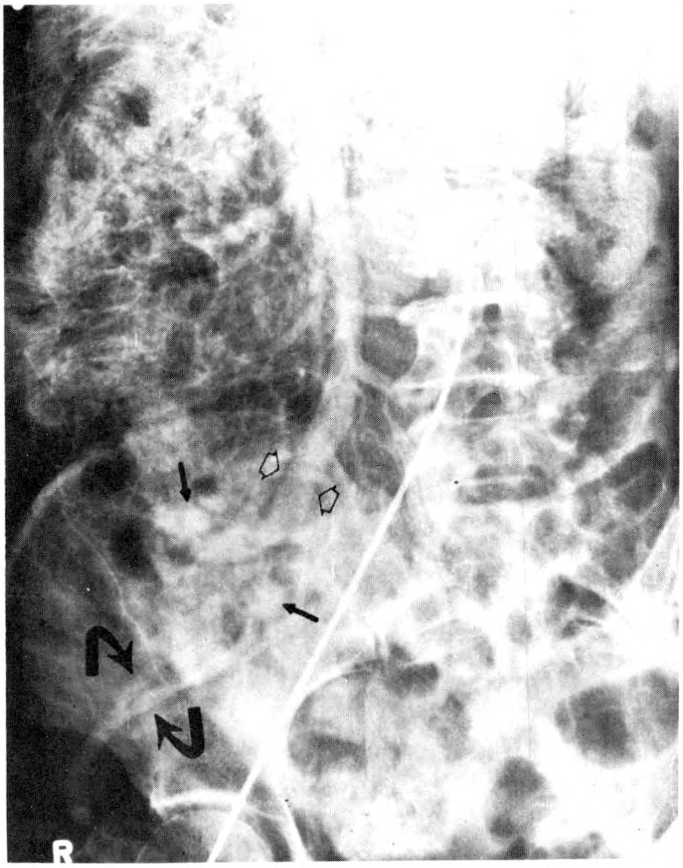

FIG. 4b. The venous phase of the superior mesenteric arteriogram shows patent superior mesenteric vein with dilated ileo-cecal vein (open arrows) and ileo-cecal varicosities (small closed arrows) which drain into a superior mesenteric vein in the pelvis thought to be the deep circumflex iliac vein (curved arrows).

the mesentery and small bowel appeared quite normal. Resection of the involved portion of small bowel was performed with an end-to-end anastomosis. Thereafter, the large dilated presumed ileocolic vein was dissected back to the base of the mesentery, and an end-to-side anastomosis performed between this vein and the right iliac vein. The liver was felt to be firm and nodular consistent with hepatic cirrhosis.

The patient's postoperative convalescence was completely unremarkable, and subsequent followup revealed no further evidence of gastrointestinal bleeding. Another admission was necessitated by an episode of hepatic encephalopathy which cleared upon administration of laxatives and enteric antibiotics (Figs. 4 a and b and 5).

Discussion

The above cases represent 6 patients who were admitted to the Massachusetts General Hospital with active gastrointestinal hemorrhage without hematemesis or recoverable blood from nasogastric aspiration. All had undergone previous intraabdominal surgery, all had portal hypertension, and at operation all were found to have large venous communications between portal and systemic venous circuits through postoperative adhesions. The point(s) of bleeding was traced to mucosal erosion over large submucosal varices within the bowel adherent to postoperative scars or adhesions.

In later cases, as this clinical entity became better defined, the preoperative diagnoses were strongly suggested by the venous phase of superior mesenteric artery angiography. When varices in unusual locations representing portal-systemic venous shunts are discovered in patients experiencing gastrointestinal hemorrhage without demonstrable source in stomach or colon, it is probable that these varices are the source of bleeding. Because the bleeding site is venous, the intraluminal pooling of dye, which is seen angiographically in the presence of arterial bleeding, is not usually evident, presumably because of dilution of dye. The reason for the preferential venous shunting through varices in adhesions is not clear.

Similar occurrences have been documented in recent literature by other investigators and provide additional information and insight into this problem. Possible physiological origins of this entity were studied in Edwards' demonstration of a network of fine communications between the parietal surface of the viscera and the posterior abdominal wall, arising in the embryo due to the juxtaposition of the developing systemic and visceral venous plexus.[3] Bloor and Orr described a patient with portal hypertension and gastrointestinal hemorrhage from a submucosal varix in the ileum formed in an adjacent adhesion.[1] This substantiates this phenomenon, as does Gray and Grollman's description of a patient treated for gastrointestinal hemorrhage by resection of ileal varices. In this patient retrograde flow from the superior

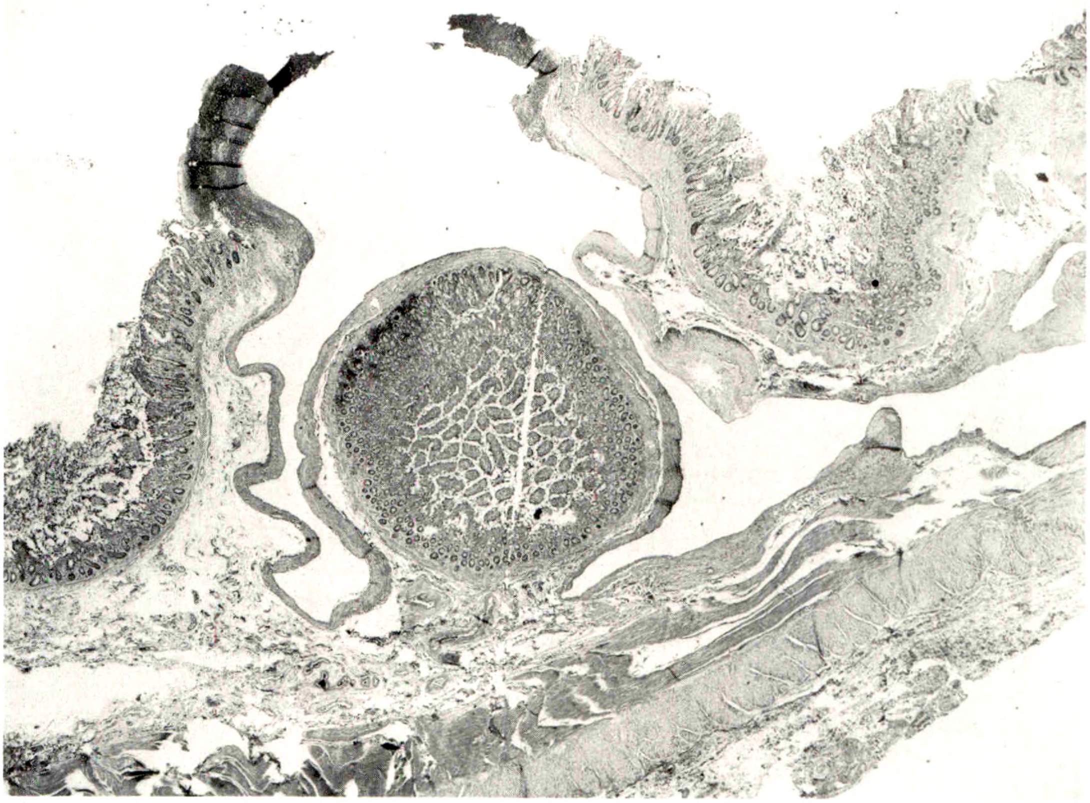

FIG. 5. The histological appearance of the submucosal varix is demonstrated in the section of resected distal ileum.

mesenteric artery into the inferior vena cava via the right ovarian vein was demonstrated angiographically.[4] A similar episode of varix-related hemorrhage was documented in a recent report by Börjesson et al. of a patient in whom ileal varices were preoperatively demonstrated by angiography. Subsequent operation revealed a large vein leading from the mesentery of the ileum via the ileal wall through an adhesion over to the lateral pelvic wall. In addition, the resected ileum contained a large submucosal varix with an opening on the mucosal side.[2]

Apparently, interruption of the adhesions and resection of the involved small bowel or construction of a portal-systemic shunt will be successful in the management of this clinical entity. Survival is probably dependent upon the patient's hepatic functional reserve. Although it is not possible to be certain on the basis of this limited experience, probably the best approach is a direct resection of the involved bowel to control the hemorrhage followed by portal-systemic decompression to prevent recurrence of portal hypertension-related gastrointestinal hemorrhage.

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Meckel's Diverticulum

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One hundred and ninety surgically documented cases of Meckel's diverticulum encountered at the Mayo Clinic during a 51-year period, 1920 through 1971, are reviewed. In 39 patients, the diverticulum was left undisturbed. In 51 patients, the diverticulum was the primary surgical disease, and, in 100 patients, the diverticulum was removed incidentally. The clinical features are presented as well as the surgical considerations. Meckel's diverticulum is a relatively frequent development anomaly with eccentric manifestations, and its surgical management has intrigued physicians for over 350 years. Dr. Charles W. Mayo stated, "Meckel's diverticulum is frequently suspected, often looked for, and seldom found."

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THE RECORDS of all patients with Meckel's diverticulum seen at the Mayo Clinic during the 51-year period of 1920 through 1971 were reviewed. Three representative groups of patients with Meckel's diverticulum were established for comparison: group 1, patients in whom Meckel's diverticulum was known to exist but was left *in situ*; group 2, patients in whom Meckel's diverticulum was the *primary* cause for surgical excision; and group 3, patients in whom Meckel's diverticulum was encountered *incidentally* and was excised.

Material and Methods

Between 1920 and 1971, 39 patients (group 1) were seen with Meckel's diverticulum that was observed incidentally at operation and left in situ. Between 1952 and 1971, 51 patients (group 2) were seen with Meckel's diverticulum as the primary surgical disease. Between 1965 and 1971, 100 patients (group 3) were seen in whom Meckel's diverticulum was observed incidentally and excised. These 100 cases represent the most recent primary and incidental surgical excisions of Meckel's diverticulum at the Mayo Clinic.

Clinical Aspects

The 190 patients in this study ranged in age from 2 days to 91 years. Seventy-two were females and 118 were males. In each case, the diagnosis of Meckel's diverticulum was established at surgery.

Presenting Clinical Features. The chief complaints prior to operation in the 51 symptomatic patients (group 2) were bleeding, abdominal tenderness, abdominal pain, obstruction, and perforation (Table 1). Technetium scans were not used for diagnosis in this series of patients.

Histopathologic Findings at Operation

The most common operations at which a diverticulum was observed and left in situ (39 cases, group 1) were gastrointestinal, genitourinary, and hepatobiliary, in descending order of frequency.

Of the 51 operations in which a diverticulum was the primary surgical disease (group 2), 11 were performed on an emergency basis, and 13 required resection of bowel. On pathologic study of the 51 diverticula, 21 were found to contain gastric or pancreatic tissue, and 4 demonstrated evidence of ulceration. Other findings in this group included a fecalith, fruit seeds, and gangrenous musoca (Table 2).

The size of diverticulum mouth in 15 specimens from females ranged 0.8 cm to 3.0 cm averaging 1.71 cm (S.D. = 0.64, S.E. = 0.16) and in 29 specimens from males ranged 0.8 cm to 6.0 cm averaging 1.97 cm (S.D. = 1.02, S.E. = 0.18).

The most common operations during which a diverticulum was observed incidentally and was excised (100

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TABLE 1. *Symptoms Before Operation (Group 2)*

Symptom	No. of patients
Bleeding (transfusions required—14)	32
Abdominal tenderness	21
Obstruction	7
Abdominal pain	35
Perforation	3

TABLE 3. *Complications After Operation in 51 Patients (Group 2)*

Complication	No. of patients
Bleeding	1
Infection	1
Abscess formation	1
Wound dehiscence with infection and phlebitis	1
Hypovolemic shock with death	1

cases, group 3) were gastrointestinal, hepatobiliary, genitourinary, and vascular, in descending order of frequency. On pathologic study of these 100 diverticula, 16 were found to contain gastric tissue, 3 were found to contain pancreatic tissue, and 2 demonstrated evidence of ulceration. Other findings in the patients in group 3 included fecaliths, enterogenous cysts, Brunner's glands, carcinoid tumor, and regional enteritis (one case each).

The average size of diverticulum mouth in 30 specimens from females ranged 0.5 cm to 4.2 cm averaging 1.87 cm (S.D. = 0.73, S.E. = 0.13) and in 48 specimens from males ranged from 0.2 cm to 5.0 cm averaging 1.63 cm (S.D. = 0.86, S.E. = 0.12).

Results

In group 1, one of the 39 patients was re-explored for bleeding the day after aneurysmectomy. At this time, a Meckel diverticulum was found to be necrotic. The patient died 6 days after the initial procedure.

In 5 of the 51 patients (group 2) who had a diverticulum excised as the primary surgical procedure, complications, consisting of wound dehiscence, infection, abscess formation, phlebitis, and bleeding, developed after the operation (Table 3).

In 12 of the 100 patients (group 3), complications developed after surgical treatment. In 3 or these 12 patients, the complication was infection. Other complications consisted of bleeding, wound dehiscence, pulmonary embolism, fistula formation, abdominal pain, obstruction, thrombocytopenia, and uremia with respiratory insufficiency (Table 4).

Discussion

The first recorded observation of an ileal diverticulum has been attributed to Fabricius Hildamus[1,2] in 1650. Subsequently, Lavater[3] reported it in 1671; Ruysch[4] published the first illustration, a copper engraving, in 1707; and Littre[5] reported its presence in a hernia in 1745. These observations were confirmed by Morgagni[6] in 1769 and by Trautner[7] in 1779. However, the first comprehensive embryologic and pathologic description of the lesion was not made until 1808 by Johann Friedrick Meckel, the younger.[8-12]

TABLE 2. *Histopathologic Findings in 51 Patients (Group 2)*

Finding	No. of patients
Gastric tissue	15
Pancreatic tissue	2
Gastric tissue with ulcer	4
Gastric and pancreatic tissue	2
Fecalith and fruit seeds	1
Gangrenous mucosa	1

Meckel first associated the diverticulum with the omphalomesenteric duct.[13] Hildamus and others had postulated the formation of the diverticulum on the basis of increased intestinal pressures.

Embryologic Factors

During the first embryonic weeks, the large ventral (entodermal) roof of the yolk sac constitutes the dorsal lining of the primitive intestinal primordium.[14-16] With growth, the primitive intestine becomes separated from the yolk sac. The area of communication narrows, elongates, and becomes the omphalomesenteric or vitelline duct, which joins the yolk sac with the intestinal tract at the junction of the foregut and the hindgut. Atrophy and obliteration of this duct normally occur by the fifth to seventh week[17] when the functioning placenta replaces the yolk sac as a source of nourishment for the fetus. The duct is normally absent by the eighth week of gestation.

Originally, a network of vessels is present on the yolk sac which converges to form paired omphalomesenteric arteries and veins. When the duct is obliterated, the only remnants of these vessels are the enteric portion from the right artery, which persists as the superior mesenteric artery, and a portion of the left vein, which is incorporated in the portal vein.

TABLE 4. *Complications After Operation in 100 Patients (Group 3)*

Complication	No. of patients
Infection	3
Infection and bleeding	2
Infection and pulmonary embolus	1
Wound dehiscence	1
Fistula	1
Abdominal pain	1
Obstruction	1
Thrombocytopenia	1
Abdominal abscess with peritonitis, abdominal pain, bleeding, uremia, and respiratory insufficiency	1

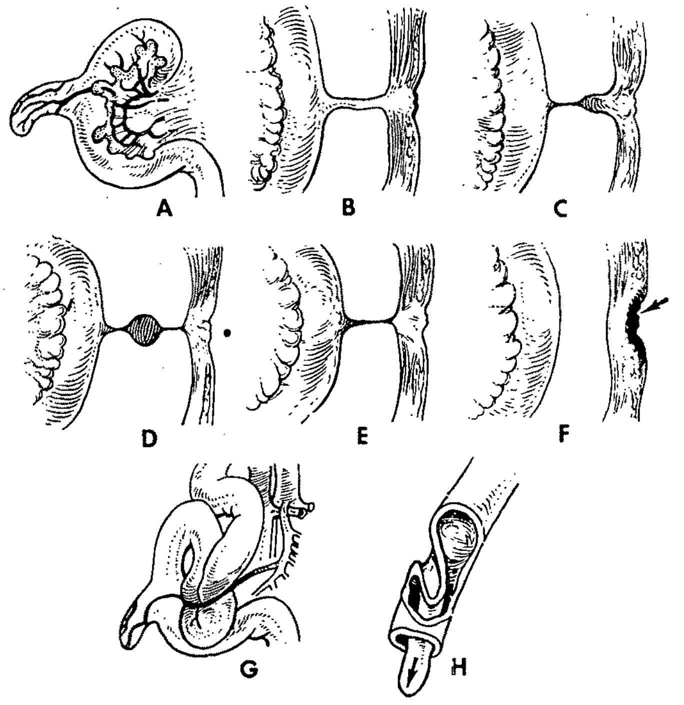

FIG. 1. Anomalies of the omphalomesenteric duct. A, diverticulum; B, complete fistula; C, incomplete fistula; D, enterocystoma; E, band; F, stawberry tumor; G, internal tumor; and H, intussusception.

Complete or incomplete persistence of the duct results in the following developmental anomalies (Fig. 1):[1,18] 1) Meckel's diverticulum; 2) complete omphaloenteric fistula; 3) incomplete omphaloenteric fistula; 4) enterocystoma; 5) fibrous band joining umbilicus to small bowel mesentery; 6) strawberry tumor of the umbilicus; 7) mesodiverticular band; and 8) intussusception. Of these anomalies, the first is the most common[19] and the last is the rarest.[20]

General Features

The incidence of Meckel's diverticulum has been reported to be between 0.3 and 4.0% at autopsy,[1,14,21–39] and between 0.14 and 4.5% at surgery.[1,9–12,15,40] When Meckel's diverticulum is found incidentally at surgery or autopsy, the incidence of the sexes is approximately equal.[41,42] However, when diverticular disease is found, excluding simple inflammation, males are afflicted more frequently than females.[42–46]

The reported size of Meckel's diverticulum varies from 1 to 56 cm in length and from 1 to 50 cm in diameter.[15,22,25,47–49] Most diverticula occur within 91 cm proximal to the ileocecal valve;[1] however, diverticula have been reported to arise from the appendix[50–52] and from the jejunum.[53,54]

Heterotropic tissue in a diverticulum was first reported of pancreatic type in 1861 by Zenker[55] and of gastric type in 1882 by Tillmanns.[56] The relationship of aberrant gastric mucosa to ulcer of a diverticulum was considered by Deetz[57] in 1907 and subsequently confirmed by many others.[19,58–93] The ratio of cases with heterotopic tissue to those with ileal mucosa has been reported to be from 1:170 to 1:10 for the pancreatic type and from 1:10 to 2:3 for the gastric type.[6,15,31,39,94–101] Other heterotopic tissues reported in Meckel's diverticulum include duodenal, jejunal, colonic, rectal, and endometrial mucosa.[29,75,102–112]

Other pathologic conditions found to be associated with Meckel's diverticulum are intestinal obstruction due to bands,[113–120] knots,[13,121–129] volvulus,[130–141] or intussusception,[23,142–170] regional enteritis,[171–174] hernia,[5,175–198] enterolith formation, and calcification,[199–226] diverticulitis,[227,228] tuberculosis,[229–232] foreign bodies,[48,233–251] parasites,[252] umbilical fistula,[26,253–270] leiomyoma,[271–286] lipoma,[284] fibroma,[284] neurofibroma,[284] angioma,[284] carcinoid,[27,287–317] adenocarcinoma,[277,318–329] and sarcoma.[272–276,330–341]

These features are supported by our study. Meckel's diverticulum is associated with a variety of pathologic conditions and must be considered in the differential diagnosis of acute abdominal situations, in all age groups.

Acknowledgment

The authors are indebted to Dr. H. M. DeBartolo, Aurora, Illinois, for his assistance.

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Burn Morbidity:

A Followup Study of Physical and Psychological Disability

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Fifty-one burn patients were studied in a retrospective manner to determine the effects of the burn injury on their ability to return to their pre-burn physical and social status. The results of this study indicate that: 1) 79% of the patients were able to return to work or school, though 45% required a change in work and 25% were not able to continue with their peer groups in school; 2) the average time of disability was 6 months; 3) there was a significant psychological morbidity as demonstrated by self-confessed depression, juvenile delinquency and divorce. There is a need for awareness of these problems so that proper counseling can be offered to the burn patient and his family both during his hospitalization and after discharge.

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NUMEROUS STUDIES concerning the acute care of the severely burned patient are available in the literature. However, these studies have emphasized the problems related to in-hospital care; namely evaluation, resuscitation, debridement, topical antimicrobial therapy and skin grafting.[5,6,13] The psychological aspects of burn injury have been recorded during hospitalization[4,6–11,14,15] but the long-term outcome of the burn patient's physical and social adjustment has not been well documented. Because of the current lack of information in this area, the burn patient is subjected to the stress of uncertainty during his early management which commonly affects his physical and psychological recovery. This problem is of particular importance in view of the improving survival statistics as a result of more sophisticated burn care.

It is the purpose of this study to document the duration of disability and the physical and psychological impairment resulting from burn injury. An attempt will be made to compare these results with the per cent of body surface burn and specifically with burns of the hands and face.

Methods and Materials

The existing files from the burn service at the University of Utah Medical Center during the years 1970–1974 were used. Data concerning the patient's age, sex, pre-burn work at school status, injury, hospital course and duration of hospital stay were extracted.

Fifty-one patients and/or one of their immediate family members were either personally interviewed by the investigators or responded to a mailed questionnaire. The questionnaire was constructed with four basic sections included in attempt to assess the physical and psychological changes. They were: 1) confirmatory data about the injury itself including degree, thickness, area and cause which had already been extracted from the patient's medical record; 2) the pre-burn status of the individual including job or school level, tendency towards depression, alcohol and drug use; 3) the post-burn status of the individual, again including job or school, depression, alcohol and drugs; 4) a comparison of the person's life activities prior to the injury with his activities since the injury. This included emotional comparison with regard to job or school work, family association, social life and physical disabilities. Evaluation also included before and after comparison of shyness, withdrawal to self and from others, marital status change and psychiatric help.

The sample included 37 males and 14 females ranging in age from one to 88 years with the distribution as demonstrated in Fig. 1. The average percent body burn was 31.2% with the frequency demonstrated in Figure 2. Table 1 reveals a breakdown of the special areas of involvement compared with total body surface burns. Fifty-seven per cent (29/51) of the patients in this study had involvement of the hands and/or face. The depth of burn was second-degree in 28% of the patients, third-degree in 15% and mixed second and third-degree in 57%. The mean duration of followup was 25.6 months post

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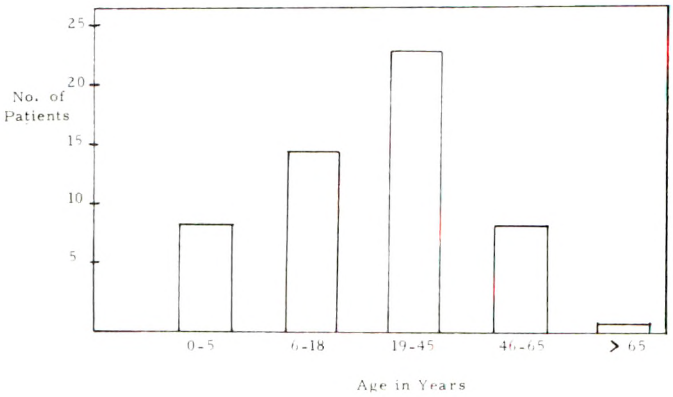

FIG. 1. Age distribution.

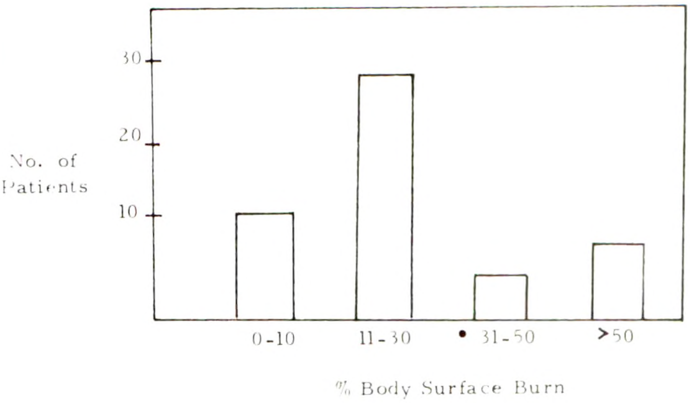

FIG. 2. Distribution by per cent body surface burn.

burn. ($\bar{X} = 25.6$; $S = 12.37$; $n = 51$). The initial hospital stay was 38.7 days ($\bar{X} = 38.7$; $S = 34.01$; $n = 51$).

Initial therapy followed the guidelines set down by the Committee on Trauma, The American College of Surgeons[3] and consisted of resuscitation using Ringers Lactate solution, but adjusted according to the patient's hourly urine output, pulse, blood pressure, central venous pressure and mental status.

Topical therapy was used with a variety of topical antimicrobial agents such as Sulfamylon Acetate, povidone-iodine (Betadine) and silver sulfadiazene (Silvadene). Hydrotherapy was instituted on a daily basis usually by the third post-burn day. Split thickness skin grafting for the areas of full-thickness burn were performed after eschar debridement and when the recipient areas were deemed ready to accept a graft. During the first three years of the study, the patients were located on a surgical ward but during the last year of the study the patients were all treated within the Burn Unit.

Results

Eight patients were not working or attending school because they were either too young or were unemployed. The results related to work or school status will therefore be based on 43 patients, 34 (79%) of whom had returned to work or school at the time of this study.

Duration of Absence from School or Work. The mean time of absence was 6.0 months. The duration of absence when correlated with per cent body surace burn is demonstrated in Figure 3 and with area of involvement in Figure 4. It should be noted that patients with burns of the face and hands had twice the per cent body surface involvement as compared to those without (Table 1).

Work Status. There were 23 patients employed at the time of their injury. Twenty-two had returned to work at the time of this study. However, of those who returned to work a significant number (10/22) required a change in their jobs (Table 2). Twenty-five per cent of those burned on the face and 37% on the hands required a change in their jobs. Of those patients without hands or face burns, 25% also required a change in their jobs.

School Status. There were 20 patients in this group ranging from kindergarten to college. Of these 20, 4 (20%) were able to continue their education with their pre-burn peer group immediately upon discharge from the hospital. In addition, 11 out of 20 (55%) were not able to return to school upon discharge from the hospital but were able to progress with home tutoring. The time required for tutoring varied from one month to two years. Therefore of the total group, 25% were unable to progress with their peers. The average per cent body surface burn of the latter group was higher than the others as demonstrated in Table 3. This subgroup was too small to determine the significance of areas of involvement.

Juvenile Delinquency. In the 6 to 18 age group, the delinquency rate was 2 out of 14 (14%). Both were male patients. This is higher than the Utah State average of 5.2% for a similar age group,[16] but is not statistically significant in this small sample size.

Divorce. Of the 19 patients who were married at the time of their injury, 5 out of 19 (26%) were divorced at the time of this study. These results are highly significant since the expected value for a similar normal population during this period of time is .71 of 19.[17]

Depression. Another striking finding of the study involved depression. Table 4 gives the results of depression change compared with the areas of burn involvement. The figures show that patients with burns of the face and/or hands have an increased incidence of depression after injury. Those without burns of the hands or face also had an increased incidence of depression but this increase was not statistically significant.

TABLE 1. *Area of Involvement vs. Ave. % Body Surface Burns*

Areas of Burn	Patients	Ave. % BSB
Face & Hands	19	33%
Hands	7	32%
Face	3	20%
Without Face & Hands	22	16%
Total	51	

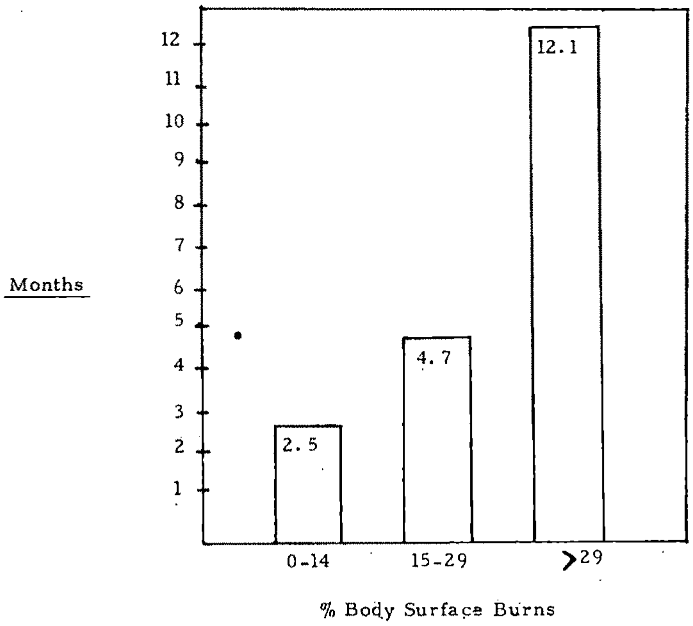

FIG. 3. Average absence from work or school versus per cent body surface burn.

TABLE 2. *Burn Injury vs. Return to Work*

	Pts.		% BSB
Total	23		
Unable to Work	1		
Returned to Work	22		
a) Same Job		12	26%
b) Different Job		10	30%

Discussion

Evaluation of physical disability in burn patients may be quite difficult because of the variety of factors that contribute to this form of disability. For example, burn scar contractures may limit motion and hinder return to work. However, medico-legal considerations and other incentive factors related to secondary gain may also prevent or hinder a patient's return to his pre-burn work status. In spite of this, some attempt was made in this study to obtain objective data relating to duration of disability and ability to return to the patient's pre-burn school or work status. We were able to document that the duration of disability was directly related to the per cent body surface burn and not specifically with areas of burn. Initially we had hypothesized that patients with burns of the face and hands had increased physical disability, but this was not confirmed in this study. The mean duration of absence from work or school for an individual with 30% body surface burns was 6 months. This was of course considerably greater in patients with burns over 30%. It was surprising to note that patients with relatively minor burns, i.e. less than 14% body surface area, had an average disability of 2.5 months. In patients who were employed at the time of their injury, it was found that 95% were able to return to work. However, 45% of these patients required a change in their jobs. Half of these patients changed their jobs directly because of their burn injury. Burns of the hands or face did not appear to influence their ability to return to work.

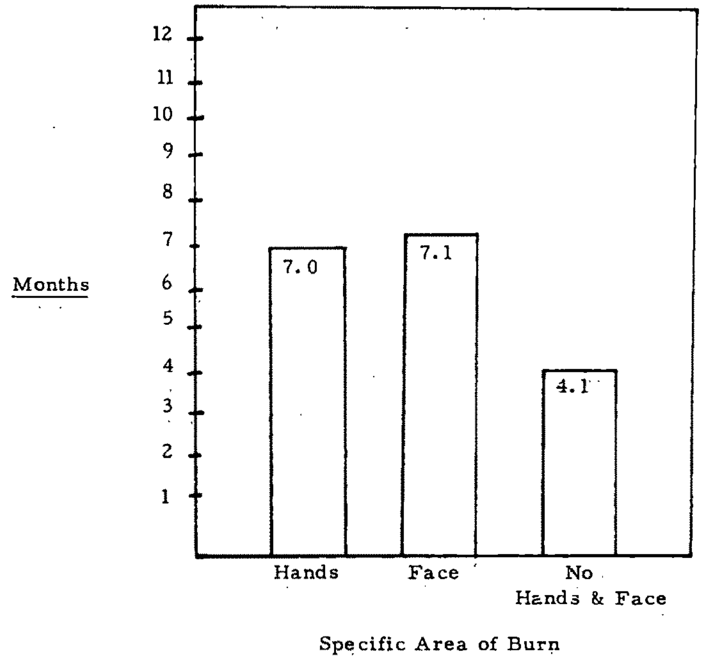

FIG. 4. Average absence from work or school versus specific area of burn.

School progression in our 20 patients indicated that 75% of the patients were able to continue with their peer groups. However, it was noted that the majority of these patients did require special tutoring in the hospital and at home so that they could re-enter school with their peer groups. The remaining 25% were significantly set back by their burn injury and, in spite of tutoring which frequently occurred at a later date, re-entered school behind their peer groups.

The social and psychological adjustments to the burn injury were the most interesting aspects of this study and revealed significant morbidity in these areas. Juvenile delinquency was noted in two out of the fourteen burned children who were between the ages of 6 and 18. This was higher than the state average for children in a similar age group. It was interesting to note that neither child had a past history of juvenile delinquency. However, both of the children came from homes in which their

TABLE 3. *School Progression vs. Per cent Body Surface Burn*

	# of Pts.	Average % BSB
Continued with Peers (without tutoring)	4	19%
Continued with Peers (with tutoring)	11	24%
Behind Peers	5	37%

parents were separated. Both patients felt rejected by their peers upon return to school and were unable to tolerate the numerous questions and teasing to which they were subjected. These two patients had relatively small burns and specifically did not have burns of the face or hands.

Divorce following the burn injury was noted in 5 out of the 19 patients (26%). Four of the 5 patients had burns of their face. However, the patients who remained married also included significant number with burns of the face (8/14). It was difficult to determine whether the burn injury was the only factor involved. For example, two of the five divorced patients stated that their marriage was deteriorating at the time of the injury. Whatever the cause, our burn patients during this brief period of followup did have a significantly higher incidence of divorce than the population at large. Our results are in contrast to Andreasen's findings in which he reported no divorces among their 20 patients.[1]

Depression was a very common finding in our patients and was noted particularly in those with involvement of the hands and face. It started at various times during the hospital course and extended for approximately one year post-burn. This was usually related to the awareness of their disfigurement, duration of hospitalization and chronicity of pain. Pre-occupation with the physical aspects of the patient's care during his hospitalization was noted in our chart reviews though occasionally concern was directed towards the psychological manisfestations. However, in spite of the in-hospital activities, the major emotional adjustment occurred after the patient left the hospital. At that time he was no longer under the constant reinforcement of the doctors, nurses and therapists but was confronted with the realities of his disability. This usually led to withdrawal, shyness and seclusion. Based on these findings, emotional support in some form should be given on a regular basis both during and after hospitalization. It was also felt that counseling should be directed towards family members and that perhaps this would have some influence in decreasing the incidence of juvenile delinquency and divorces. It should be noted, however, that the majority of patients reported a decrease in their depression at approximately one year post-burn and were able to resume their pre-burn social activities. This was also observed by Andreasen, et al. in their study.[2]

Although a relatively small sample was surveyed, certain trends were evident from this study. Physical disability appears to be correlated to total per cent body surface burn and not to specific areas of injury. Social adjustment (juvenile delinquency and divorce) does not appear to correlate with per cent body surface burns or specific areas of involvement. Perhaps pre-burn personality traits are more important in influencing social adjustment. Post-burn depression does correlate with duration of disability, per cent body surface burn and specific areas of involvement. Unfortunately the small group studied does not allow separation of the direct influences of each of these three variables. However, burn patients indeed have varying periods of disability which may interfere with their physical and social adjustments to the people and world around them.

TABLE 4. *Depression Change After Burn Injury*

	Greater	No Change	Less	
Face and Hands	24	5	0	P < 0.001
Not Face and Hands	14	0	8	n.s.
	38	5	8	P < 0.01

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The Effects of Femoropopliteal Vein Graft Failure on Limb Function

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Twenty-one patients were followed for an average of 40 months following occlusion of femoropopliteal vein grafts. Serial recordings of the resting ankle pressure index and treadmill walking time were correlated with the patient's clinical status, and compared to the preoperative values. Graft failure resulted in a return to preoperative status in ten of 11 limb salvage patients. There were 5 amputations, 3 died of unrelated causes, and 2 were subsequently improved by further reconstructions. At last followup, 3 of 10 patients who were operated on for claudication were unchanged, 6 were improved, and one became worse. In no case did graft failure result in the development of advanced ischemia. Femoropopliteal graft failure did not have a significantly adverse effect on limb function or survival in patients presenting with claudication, nor did it complicate the subsequent course of patients in whom the initial aim was limb salvage.

THE REVERSED saphenous vein bypass is generally regarded as the operation of choice in the treatment of atherosclerotic occlusive disease of the femoropopliteal segment. Nevertheless, controversy continues regarding the indication for operation, particularly for the patient in whom claudication alone rather than advanced ischemia is the presenting problem. Much of the debate is concerned with the possible role played by femoropopliteal reconstruction in the development of distal disease, and with the effect that graft failure may have on the eventual outcome of the limb. Objective data remain scarce, and the present study was undertaken to determine the consequences of graft failure for limb function and survival.

Materials and Methods

The study includes 21 male patients between the ages of 41 and 78 years (average 57). They comprise all the failures, both early and late, of a series of 62 consecutive reversed saphenous vein femoropopliteal grafts in which the cumulative patency rate was 50% at 5 years. Ten of these patients had intermittent claudication as the only symptom, while 11 demonstrated signs and symptoms of more advanced ischemia such as rest pain or tissue necrosis. Atherosclerosis was the underlying disease in all.

All patients received common femoral to popliteal grafts. In ten cases the popliteal anastomosis was constructed above the knee, and in 11, below the knee. Patency ranged from one day to 112 months in the claudication group (average 19 months), and one day to 108 months (average 16 months) in the more ischemic group. None of the patients underwent lumbar sympathectomy.

Patients were examined at intervals of 3 to 10 months both before and after graft failure. Each visit included a pertinent history and physical examination. After the patient had rested for 15 minutes, supine systolic ankle and brachial blood pressures were measured with pneumatic cuffs and a Doppler flow detector, as has been described previously.[13] When possible, the response of the ankle pressure to treadmill exercise was evaluated. The resting ankle pressure indices (ankle systolic blood pressure divided by brachial systolic blood pressure) were calculated in order to avoid variation related to changes in systemic blood pressure.[14]

Group results were compared with preoperative parameters and subjected to analysis by the paired T-test. In addition, a patient was considered to have been improved or made worse if his resting ankle pressure index was increased or lowered by 10% of the preoperative value.

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TABLE 1. *Followup Data for Patients with Intermittent Claudication*

Patient	Duration of Post-Occlusion		Resting Ankle Pressure Index*				Clinical Status, Current as Compared to Pre-Operative
	Patency (Months)	Followup (Months)	Preop	Postop	Graft Failure	Last Visit	
1	<1	8	76	82	76	79	Unchanged
2	<1	94	40	75	38	58	Improved
3	4	100	70	77	56	79	Improved
4	5	30	62	86	23	57	Unchanged
5	5	74	51	98	49	58	Improved
6	6	61	64	67	58	82	Improved
7	7	13	57	86	38	42	Worse
8	10	1	53	85	49	49	Unchanged
9	37	<1†	62	101	43	110†	Improved
10	112	11	38	70	53	58	Improved

* Ankle systolic pressure ÷ systolic pressure.

† Reoperated successfully, remains patent 17 months postoperatively.

Results

Immediately after the grafts occluded, 6 of the 10 claudicants were unchanged compared to their preoperative status (Table 1). Although 4 were worse, one of these was improved by immediate reoperation. Two others have subsequently improved spontaneously. Only one patient remains worse at last followup, with a significantly decreased resting ankle pressure index and increased claudication. No patient has developed more advanced ischemia during a followup period of up to 100 months (average 40 months).

In Figure 1 are shown the mean resting ankle pressure indices of the 10 claudicants preoperatively (56.8 ± 4.3 SEM), postoperatively (80.7 ± 3.2 SEM), at the time of graft failure (48.9 ± 5.0 SEM), and at the last visit (62.4 ± 4.7 SEM). When paired data for each patient are analyzed, there is no statistical difference between the preoperative ankle pressure index and the ankle pressure index either at the time of graft failure or at the last followup visit. The observed improvement after operation is significant ($P < 0.005$), as is the improvement between the time of graft failure and the last visit ($P < 0.01$).

Data for the group with advanced ischemia are compiled in Table 2. Of the 11 patients, 7 were early failures (within one month of operation), and two of these eventually underwent major amputation. One (patient 15), had a simultaneous ilioprofunda endarterectomy and remained improved despite graft failure, and another (patient 17) was subsequently improved by a similar procedure. One man continued to have rest pain and died 6 weeks postoperatively. The last patient maintained a full-thickness skin graft despite vein graft failure.

There were four patients with late occlusions. Two had amputations below the knee, one continued to have rest pain and died one year later and one has a recurrent ischemic ulcer.

There were no operative deaths in the series, either at the time of the initial reconstructions, or with any subsequent amputation.

Comment

There continues to be disagreement regarding the role of femoropopliteal revascularization, particularly as applied to the patient whose sole complaint is claudication. Such patients have at most a 7% risk of amputation

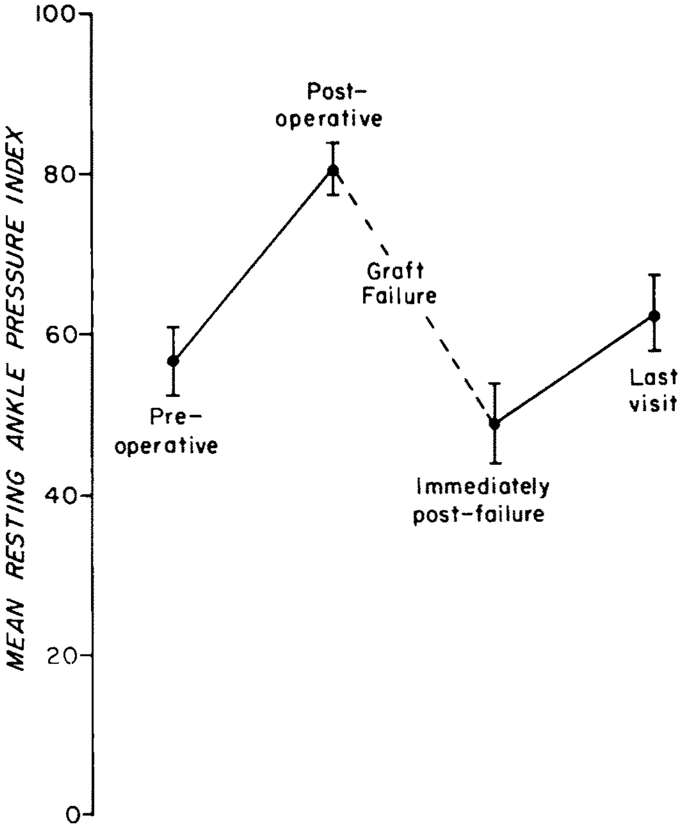

FIG. 1. Resting ankle pressure indices (mean ± 1 S.E.M.) of the patients presenting with intermittent claudication. Patient 9 is excluded.

TABLE 2. *Followup Data for Patients with Advanced Ischemia*

Patient	Graft Patency (Months)	Post-Occlusion Followup (Months)	Resting Ankle Pressure Index			Current Index and Clinical Status
			Preop	Postop	Graft Failure	
11	1	1	63	—	—	Below-knee amputation
12	1	1	54	85	58	Died with rest pain*
13	1	1	62	—	40	Toe amputation, later died*
14	1	2	35	55	26	Below-knee amputation
15	1	6	0	—	38†	Improved, later died*
16	1	49	63	—	55	60, healed ulcer
17	1	107	27	77	18	42, improved‡
18	3	1	0	100	—	Below-knee amputation
19	24	1	0	92	0	Below-knee amputation
20	57	1	54§	78	38	38, recurrent ischemic ulcer
21	108	12	26	73	29	Died with rest pain*

* All deaths were beyond 30 days postoperative, and of unreleated causes.
† Simultaneous ilio-profunda endarterectomy.
‡ Subsequent ilio-profunda endarterectomy.
§ Below-knee systolic pressure.

within 5 years,[1] and the risk may be as low as 2.5%. The majority do well with only moderate disability. Because of this relatively low incidence of limb loss and significant disability, it is incumbent upon the surgeon to show that graft failure will not worsen the preoperative status and prognosis, and particularly that it will not result in advanced ischemia.

Two brief case reports may serve to illustrate some of the points which are at issue.

Case Reports

Patient 4, age 45, had right calf claudication at one block and a superficial femoral occlusion. A femoropopliteal bypass was done in September 1971, and subsequently failed in May 1972. Fig. 2 is a graph of the resting ankle pressure index versus time, current to the last followup visit in November 1974. The observed marked drop in the ankle pressure index at the time of graft failure was shown by segmental pressure gradients to be associated with increased disease in the popliteal and tibial segments. He has since improved to the extent that he is able to walk one-half mile with ease, and his ankle pressure index has returned to approximately the preoperative value.

Patient 10 had a left femoropopliteal bypass in October 1964 at the age of 62, for treatment of one block claudication secondary to a superficial femoral occlusion. As seen in Fig. 3, at the time of graft failure 112 months later his ankle pressure index remained well above the preoperative value. Segmental pressure gradients reveal no evidence either of disease progression at any level, or of collateral regression.

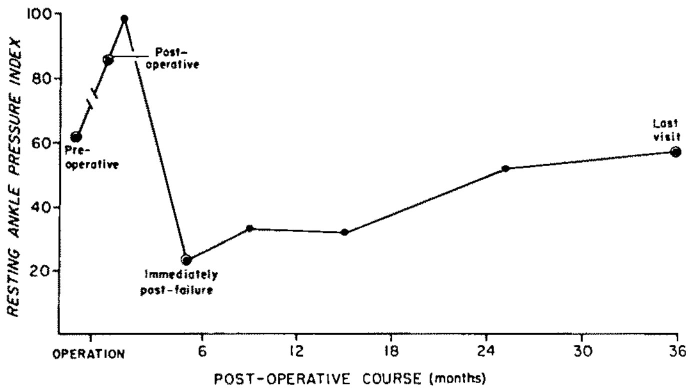

FIG. 2. The course of Patient 4 as assessed by the resting ankle pressure index. Although an initial fall occurred in the index subsequent to graft failure, the patient has since made a steady recovery and is now virtually asymptomatic.

Discussion

It has been observed[3,9] that disease progression following revascularization tends to occur distal to the graft. Such progression has been related to normalization of the distal arterial pressure, and has in turn been implicated as one cause of eventual graft failure. Graft occlusion, however, has not uniformly been followed by a worsening of the preoperative status. Stoney et al.[12] reported deterioration in 3 of 7 patients, two of whom required amputation. DeWeese[5] reported increased claudication in four of 14 patients. On the other hand, Miller[8] has recently reported a series of 28 graft failures, none of which led to increased symptoms.

In the present study four of 10 claudicants were initially worsened over their preoperative status. However, at last followup only one remains so. Of the other 9, 6 have improved as compared to their initial conditions, and 3 are unchanged. Only Patient 4 demonstrated definite evidence of significant distal disease progression, and in spite of this he has made a steady improvement since the time of graft occlusion. On the other hand, Patient 10, with the longest graft patency, demonstrated no evidence of disease progression at any level whatsoever.

A further argument against femoropopliteal reconstruction maintains that the collateral circulation may be irreversibly damaged, either through direct operative trauma or by involution, leaving the limb worse off if the graft should fail. The former can be avoidable with careful operative technique. With regard to the second risk factor, the fate of the collateral circulation in a previously chronically ischemic human limb which has undergone a successful revascularization is largely unknown. In the acute dog model, collaterals have been shown to respond relatively quickly, acting within minutes to substantially increase volume flow to ischemic tissues in cases of sudden temporary proximal occlusion.[11] This response may decline almost as quickly after resumption of normal flow. In a chronic dog model Jacobson[7] demonstrated that the collateral circulation tends to involute after continuity of the obstructed vessel is restored. Implicit in his data, however, was the observation that collateral function returned relatively quickly when the main vessel was again obstructed. Although caution must be exercised in the application of animal data to the clinical situation, the suggestion that the collateral bed does not entirely regress is supported by the data in Table 1. As noted earlier, there is no significant difference between the ankle pressure indices of the group preoperatively and those at the time of graft failure. In addition, most of the patients demonstrated further improvement. This suggests not only that the collaterals did not significantly involute, but that their development has resumed. This was best illustrated in Patient 10. Therefore, the bulk of the evidence, experimental and clinical, would indicate that a carefully done reconstruction need not have a permanently deleterious effect on pre-existing or future collateral beds.

The experience with the patients with advanced ischemia, 5 amputations in 11 cases of graft failure, is similar to that of other investigators. Five other patients reverted to their preoperative conditions. Nevertheless, one man (Patient 16) has maintained a successful full-thickness skin graft which was placed during the period of graft patency. Several attempts at skin grafting had failed prior to the femoropopliteal reconstruction.

When the surgeon contemplates an attempt at limb salvage, two considerations are of prior importance. First, that the operative mortality should not exceed that of primary amputation, and second, that the level of amputation should not be adversely affected by a failed attempt at reconstruction. There is ample evidence in the literature[4,6] to indicate that the mortality of a major amputation is at least as high as that for a femoropopliteal reconstruction, particularly in the elderly. There were no operative deaths in the present series. The second point is open to more dispute. However, Burgess and Marsden[2] have demonstrated that failure of a prior reconstruction need not result in a higher major amputation level, although wound complications are more frequent and the clinical course is often more protracted. In the present series each of 4 major amputations was successfully carried out at the below-knee level, despite the fact that all had below-knee popliteal anastomoses.

In summary, in this series of objectively studied patients failure of a femoropopliteal graft done for intermittent claudication generally did not result in a prolonged adverse effect on the functional status of the limb, and as far as could be determined did not adversely affect the ultimate prognosis for limb survival. Similarly, patients presenting with advanced ischemia reverted to their preoperative status following graft failure, with no appreciable worsening of their situations.

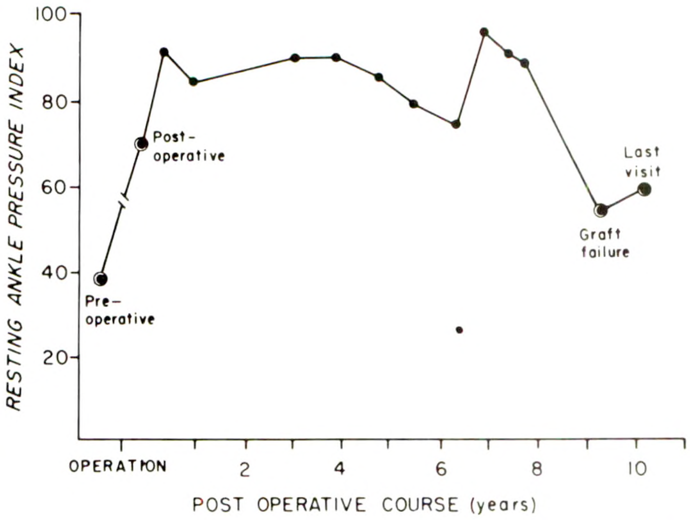

FIG. 3. The course of Patient 10 as assessed by the resting ankle pressure index. The index remained well above the preoperative value despite graft failure. There is no evidence of disease progression or collateral regression.

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Lower Extremity Ischemia After Femoral Arteriovenous Bovine Shunts

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Use of bovine carotid artery grafts for femoral arteriovenous fistulas is now an accepted method of circulatory access for patients who require chronic hemodialysis. A serious but infrequently mentioned complication of this technique is lower extremity ischemia secondary to an arterial steal phenomenon. Three cases of this syndrome are presented and specific recommendations made for preoperative and intraoperative evaluation in order to avoid this complication. A possible surgical technique for correction of this syndrome is also discussed.

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THE INCREASED survival rate of patients on long-term renal dialysis and the acceptance of patients with multiple systemic diseases have led to serious problems with vascular access. Currently, the external shunt and arteriovenous fistula are the primary methods of access. When these techniques are unsuccessful, many surgeons turn to bovine carotid artery shunts. Rosenberg et al.[4] were the first to report their experience with enzymatically treated bovine carotid arteries in dogs. Subsequently, these investigators reported their first experience with the use of the graft in man.[5]

Although these grafts were used originally as arterial prostheses for reconstruction of limbs with arterial insufficiency, their rise as sites for vascular access for chronic hemodialysis patients has only recently been appreciated. Several recent reports in the literature attest to their efficacy. However, as experience with these grafts increases, serious complications are being reported. Merickel et al.[3] reported on 100 patients with bovine shunts in the upper extremity for vascular access, the largest series in the literature. Their complications included infection, hematomas, false aneurysms, edema, pseudodiaphragms, and pseudointernal formation with dissection.

Another important complication not noted in their study is arterial steal syndrome. Bussell et al.[1] and Haimov et al.[2] reported on upper extremity ischemia after arteriovenous fistula and bovine grafts; however, Zincke et al.[6] reported the only case of lower extremity arterial steal syndrome secondary to a bovine graft. The three case reports presented herein and the discussion of this potentially serious complication emphasize methods of surgical correction and prophylactic measures to be taken at the time of the initial operation.

Methods and Materials

The bovine grafts had been implanted for purposes of hemodialysis. Graft size varied from 7 to 8 mm in diameter and from 37 to 40 cm in length. They had been anastomosed to the common femoral artery and common femoral vein in an end-to-side fashion. (The length of the anastomosis varied from 1.5 to 2.0 cm depending on the size of the recipient vessel.) The bovine graft formed a loop in a superficial subcutaneous tunnel on the anterior thigh.

The records of 170 patients who received femoral arteriovenous bovine shunts (FAVBS) were reviewed for evidence of arterial insufficiency to the lower extremity. Three patients with the symptomatology and physical findings of severe arterial steal syndrome were identified.

Case Reports

Case 1. A 64-year-old non-diabetic woman with chronic renal failure and chronic hemodialysis secondary to nephrosclerosis since 1970 and congestive heart failure since 1968 was admitted for a vascular access procedure. On physical examination, she was noted to have good peripheral pulses of the upper and lower extremities.

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She had had several arteriovenous fistulas and arteriovenous shunts of the upper extremity. Because of decreasing flow in her brachial artery to brachial vein saphenous graft, a left FAVBS* was inserted, forming a loop on the anterior thigh. Postoperatively, the shunt was noted to be working well. However, within a few hours the patient started to complain of severe pain and swelling of her lower extremity; the distal pulses to that extremity were noted to be absent. On the first postoperative day, an angiogram showed that the shunt and femoral artery were patent. The shunt was removed and the artery reconstructed. However, pain and swelling of the lower extremity persisted and pulses did not return. Symptoms were attributed to severe swelling secondary to the ischemia. Foot drop had also developed. Anterior and posterior compartment fasciotomies were performed.

Postoperatively, distal pulses returned, and swelling gradually subsided. Six months after operation she was noted to have good pulses and viable skin, but a partial motor and sensory loss was present.

Comment: Although several segments of femoral artery narrowing were demonstrated on arteriogram, the patient was asymptomatic and had distal pulses preoperatively. Thus, she had probably not developed collaterals to her lower extremity, and the stenotic areas in her femoral system became critical stenoses when the perfusion pressure was lowered by creation of the arteriovenous shunt. The ischemia produced by the "steal" threatened the viability of the extremity, and although corrective measures were taken, permanent disability resulted.

Case 2. A 49-year-old non-diabetic woman with chronic renal failure secondary to chronic pyelonephritis had required chronic hemodialysis for three years prior to admission. On physical examination, she had good pulses of the lower extremity and evidence of a clotted bovine shunt of her left arm. A left FAVBS was inserted. Postoperatively, pulses to the distal left extremity were absent. However, when the graft was occluded, these pulses returned. Over the ensuing few days, decreased sensation and occasional numbness of the left leg developed. Two weeks postoperatively, an ischemic ulcer over the head of the left first metatarsal was noted, and there was drainage from the left groin incision. However, an angiogram showed no evidence of a false aneurysm and demonstrated that bovine shunt and femoral artery were patent (Fig. 1).

Ten weeks postoperatively, a false aneurysm of the bovine shunt ruptured and the shunt was excised and the femoral artery reconstructed. Pulses to the left lower extremity returned, and the patient's symptoms of ischemia disappeared. A right FAVBS was subsequently inserted without loss of the distal pulses and without development of symptoms of ischemia.

Comment: Although the patient had good peripheral pulses preoperatively, after placement of the left FAVBS, ischemic symptoms developed, and her distal pulses were not palpable. When the shunt was removed, the pain disappeared and the pulses returned. It is interesting that she was able to tolerate a right FAVBS without ischemic signs or symptoms. This implies that a localized iliofemoral occlusion rather than myocardial or generalized aortic disease may determine the extremity which is at risk.

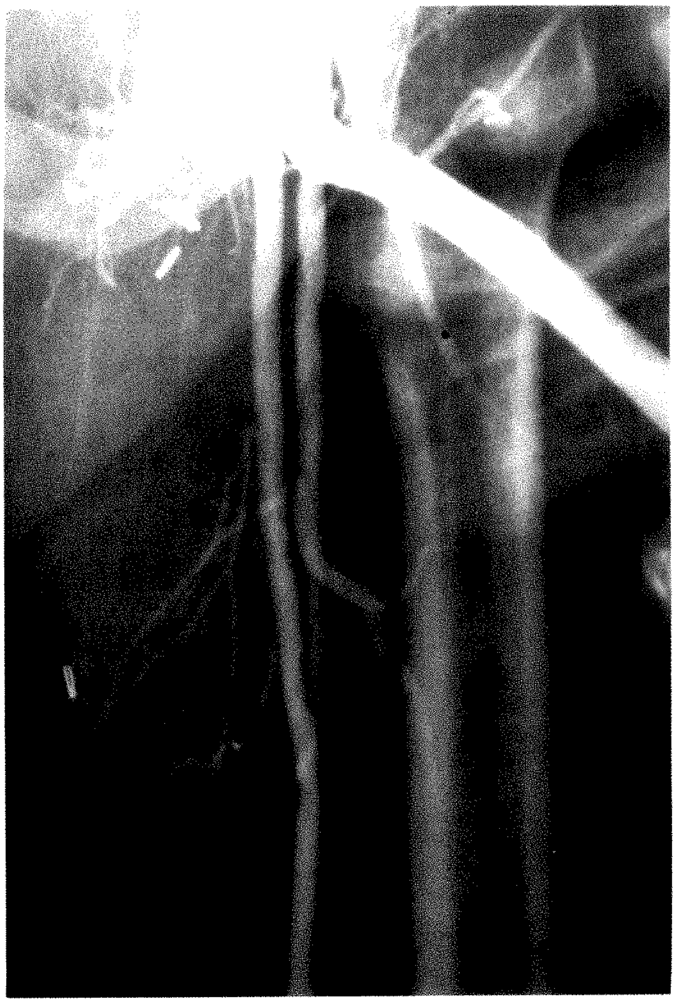

FIG. 1. Arteriogram (Patient 2) demonstrating patent graft and superficial femoral artery.

Case 3. A 33-year-old juvenile diabetic hypertensive woman with chronic renal failure and chronic hemodialysis secondary to the diabetes was admitted for placement of an FAVBS. She gave no history of claudication and had good distal pulses in both lower extremities. She underwent a left FAVBS without incident. However, on the ninth postoperative day, she noted intermittent claudication of the left calf and was found to have absent left distal pulses. An arteriogram revealed partial arteriosclerotic occlusion of the left superficial femoral artery (Fig. 2) without evidence of thrombosis or embolism. Doppler pressure measurements showed substantially lower pressures in the left leg that returned to normal on manual occlusion of the bovine shunt (Table 1). The groin incision was opened, and flow in the bovine shunt was measured at 2800 cc/min. This was reduced to 200 cc/min with a dacron band. Postoperatively, she was asymptomatic; her left distal pulses were palpable, and her left Doppler pressures returned to normal. Unfortunately, the bovine shunt subsequently thrombosed.

Comment: This patient illustrates the difficulty with banding the bovine shunt in the steal syndrome. Had the flow not been decreased so markedly, perhaps the thrombosis would not have occurred. However, tur-

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* Femoral arterial venous bovine shunt.

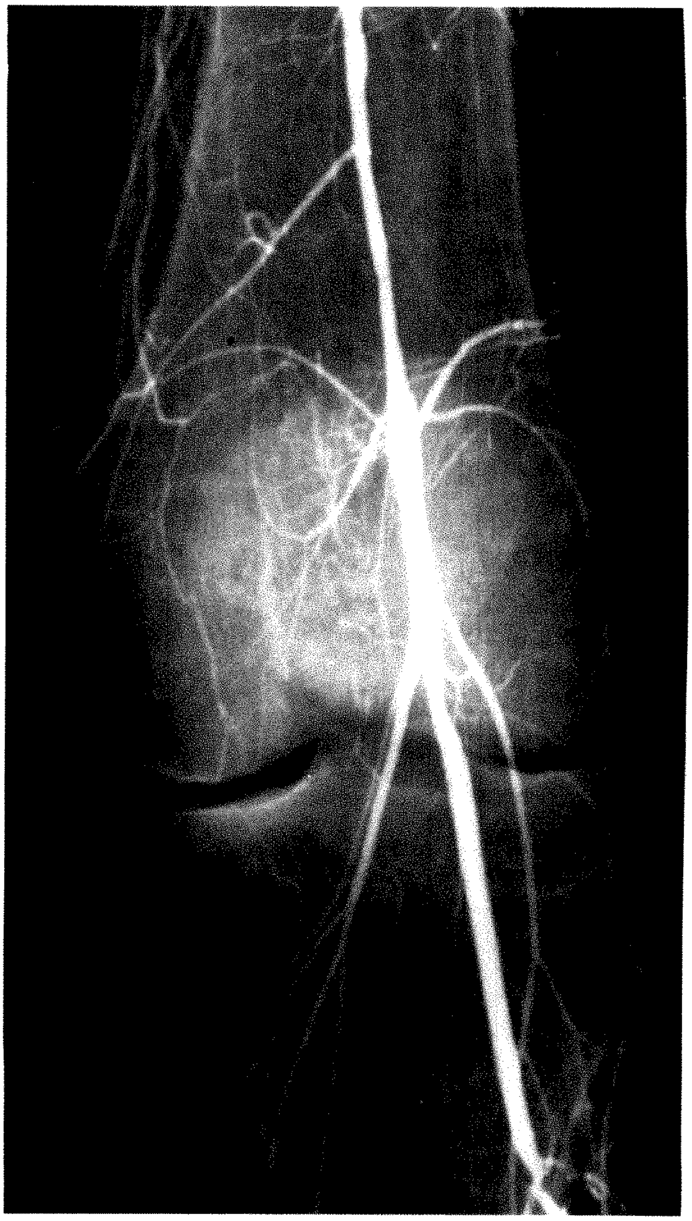

FIG. 2. Arteriogram (Patient 3) demonstrating the critical stenosis in the superficial femoral artery.

bulence caused by the band may be the etiologic factor even when flow is adequate.

Discussion

Arterial insufficiency of the lower extremity secondary to a FAVBS is a serious problem. Most patients on chronic renal dialysis have severe atherosclerosis and, thus, are susceptible to this complication. Many of these patients have signs of claudication preoperatively and obviously are poor candidates for a femoral shunt. However, many patients are asymptomatic with moderate to severe occlusive disease of the femoral arteries. These patients are at risk when the perfusion pressure is lowered by shunting of flow through the femoral vein. This lowered perfusion pressure allows the stenotic area to become a critical stenosis, and flow to the leg is diminished substantially. Arteriograms for Patients 1 and 3 showed no stenosis at the suture line, and contrast medium was visualized in the graft and the femoral artery distal to the anastomosis (Fig. 2). However, there was plaque in the distal superficial femoral artery.

TABLE 1. *Doppler Pressures on Patient 3*

	R Side	L Side Graft Open	L Side Graft Occluded	L Side Graft Banded
Wrist	140 mm Hg	140 mm Hg	140 mm Hg	164 mm Hg
Thigh	190 mm Hg	110 mm Hg	180 mm Hg	180 mm Hg
Calf	140 mm Hg	80 mm Hg	150 mm Hg	156 mm Hg
Ankle	130 mm Hg	60 mm Hg	120 mm Hg	140 mm Hg

The shunt can markedly decrease the pressure in the distal arterial system, as all three patients lost their distal pulses after operation, and these returned when the grafts were removed. Doppler findings in Patient 3 documented the markedly decreased pressure in the left lower extremity as compared to the right; with the shunt occluded, they returned to normal.

In Patient 3, the intraoperative flow of 2800 cc/min through the shunt indicates a large left-to-right shunt. The significance of this shunt can be appreciated when one notes that with banding to decrease the flow to 200 cc/min, the Doppler measurement of the left lower extremity returned to normal, and the patient became asymptomatic.

To avoid arterial insufficiency of the lower extremity secondary to FAVBS, certain screening procedures should be used. The patient should be carefully interviewed for any symptom of rest pain or claudication, and a walking tolerance test should be performed. Doppler pressures of the lower extremities will help to delineate any occult lesion that may be present. Roentgenograms of the extremity should be obtained to screen for calcification of the distal arteries, indicating severe disease. Finally, nerve conduction studies should be obtained to define baseline deficits secondary to uremia or diabetes. If the above examinations do not identify the patient as a significant risk and a FAVBS is performed, intraoperative flows and Doppler pressures should be obtained. These flows can then be adjusted to satisfactory levels with banding of the shunt or use of a graft smaller in diameter. Flows of 500 cc/min are adequate for dialysis and should maintain graft patency. If the patient becomes symptomatic postoperatively, the walking tolerance test, Doppler pressures, and nerve conduction studies should be repeated. The majority of renal dialysis patients will tolerate a bovine carotid artery shunt without evidence of arterial insufficiency. The incidence in our series of FAVBS was low. With proper screening and intraoperative precautions, it may be possible to eliminate this complication entirely.

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Corticosteroid Treatment of Experimental Smoke Inhalation

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The effect of four corticosteroid analogs was evaluated in the treatment of smoke inhalation injury. Rats were exposed to white pine smoke for 15 minutes at 25 C, in a specially designed smoke apparatus. Methylprednisolone, 10 mg bid × 2d, starting one hour post exposure, was most effective in reducing expectant mortality (22.6%). A single injection of methylprednisolone, 20 mg, at one hour, resulted in a 76.7% reduction. There was no significant difference between the single injection of methylprednisolone and dexamethasone, 4 mg, but the administration of analogs with primarily mineralocorticoid activity, cortisone and hydrocortisone, actually increased mortality. In the control rats, marked interstitial edema occurred by 24 hours, the absence of which following treatment correlated closely with the results of the mortality study. This suggests that post exposure death due to white pine smoke is a result of direct lung injury, with increased endothelial and alveolar membrane permeability and edema, and that administration of glucosteroids in massive doses was effective in reducing this permeability and resultant edema.

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THE LETHAL EFFECTS of smoke inhalation have been known since the days of Pliny, when he reported that prisoners were executed by placing them over green wood fires, yet little actual concern was paid to smoke inhalation until the Cocoanut Grove fire in 1942. At that time, patients without cutaneous burns were triaged into the minimal category, only later to be found dead of unexplained causes.[1,2,9,13] But real concern has only recently occurred when it was revealed that pulmonary complications following thermal injury result in most deaths attributed to burns.[6,7]

Clinically, the treatment of these respiratory complications has been non-specific, such as administration of oxygen and humidity, or the correction of blood gas or acid-base abnormalities. The only specific prophylactic or therapeutic treatment has been the administration of corticosteroids, usually methylprednisoline, frequently in massive amounts, and in varying dose schedules.[7,8,11,12] However, at the present time no definitive laboratory or clinical data exist as to the efficacy of these potent drugs, and corticosteroid insufficiency has not been established in patients with a thermal injury.

In "Metabolic Care of the Surgical Patient," published in 1961, Moore stated, following a long discussion of the indications of corticosteroids, "If the clinical appearances cannot be accounted for on any basis other than adrenal failure, the results of more time consuming tests is not awaited."[5] The patient is then treated with corticosteroids. Since 1961, this philosophy has dominated the practice of medicine. For whatever good, no patient should die without having the "benefit" of steroid therapy! The present ready availability of these agents has resulted in the administration of massive doses. Are they effective? What about the side effects?

The reduction in neutrophils is well-documented, and our laboratory has recently reported a marked increase in pulmonary bacterial susceptibility following the reduction in the number and function of alveolar macrophages following even short-term steroid therapy.[10] Similarly, we have also shown that considerable differences in susceptibility result following the use of various steroid analogs when compared to their generally accepted anti-inflammatory equivalents.

During the past 5 years, our laboratory has developed a rat smoke inhalation model by specially designing an apparatus whereby the amount, composition, and temperature of varying types of smoke could be produced, and the animals exposed in a completely controlled atmosphere chamber, while continuously monitoring

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gases and temperature. In addition, during and following exposure, the animals rectal temperature, electrocardiogram, respiratory rates, and blood gases can be monitored. The rats, Sprague-Dawley derived, have been bred in-house, and are completely free of murine typhus, a necessary requirement in this type of inhalation research.

It was the objective of this study to evaluate the effect of four commonly used corticosteroid analogs on the mortality rate, and pathologic findings following the exposure of rats to white pine smoke.

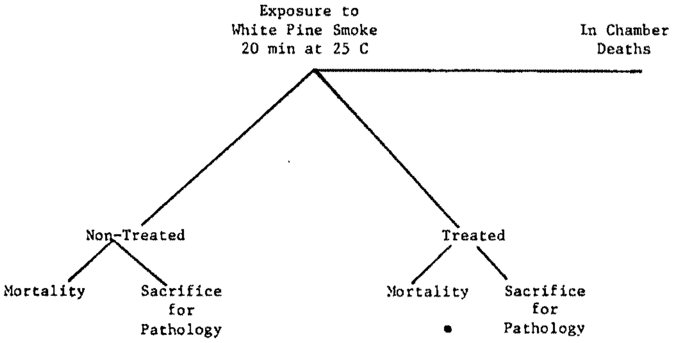

FIG. 1. Experimental design of each run showing the division into treated and untreated groups of the survivors.

Method

The experimental design is shown in Fig. 1. Six hundred and forty-seven albino female Sprague-Dawley Rats, bred and raised in our vivarium, and weighing between 180–200 grams, were exposed to white pine smoke produced in the controlled atmosphere chamber apparatus previously reported.[4] The fuel load in the combustion chamber consisted of 100 grams of white pine wood (9 × 6 cm; 0.8 cm thick), which was ignited by exposure to radiant heat. Smoke was allowed to cool to 25 C before entering the animal exposure chamber at a rate of 250 l/min. Sixteen animals at a time were placed, unanesthetized and unrestrained, in individual cages in the animal exposure chamber. Smoke was not allowed to recirculate, but was instead vented directly from the animal exposure chamber to the outside. This "open system" allowed for the constant addition of outside air to the apparatus. The exposure period began as soon as the wood ignited, and lasted for 20 minutes.

Table 1 shows the distribution of the various treatment groups. All treatments began one hour following removal of the animal from the exposure chamber, and were given twice daily for two days, in the methylprednisolone 5 mg group (5 mg bid × 2d), and the methylprednisolone 10 mg group (10 mg bid × 2d). In the four other groups, the various analogs, methylprednisolone, dexamethasone, cortisone, and hydrocortisone, were given as a single injection one hour post exposure, in the generally accepted anti-inflammatory dosage, i.e., 20 mg, 40 mg, 80 mg, and 100 mg. All animals were kept in individual cages in air-conditioned rooms for 15 days. During this period, animals were given Purina rat chow and water *ad libitum*, but no other medication or treatment.

All animals were sacrificed by guillotine method in order to preclude the possibility of pulmonary edema being induced by anesthesia.

Results

The combined mortality of those 232 animals which survived the actual exposure, but were not treated, was 107 animals, or 46.12%. The effect of the various treatments, however, could only be ascertained by comparing the results in each treatment group with the untreated controls in the same exposure runs, as seen in Tables 2 and 3.

The dose response of methylprednisolone (Table 2) illustrates the effects of two different doses given on the same dose schedule, and a third dose given in a single massive injection. The administration of methylprednisolone 5 mg bid × 2d resulted in the deaths of 26.7% of the animals, as compared to 34.5% in the accompanying controls. A dose of methylprednisolone 10 mg bid × 2d resulted in a 15% mortality, instead of the 64.5% in the untreated controls for the group. When a single injection of methylprednisolone (20 mg × 1d) was given one hour post exposure, mortality was 14.9% compared to 53% in the untreated controls. No significant alteration in the average time of death was found in any of the groups.

When the other three analogs were compared in the

TABLE 1. *Experimental Design Showing the Number of Runs, the Total Number of Rats, and the Number of Animals Sacrificed for Pathologic Studies in Each Treatment Group*

Treatment	Number of Runs	Number of Rats	Number Sacrificed for Pathology
Methylprednisolone 5 mg bid × 2d	6	72	4
Methylprednisolone 10 mg bid × 2d	7	103	4
Methylprednisolone 20 mg × 1d	10	146	4
Hydrocortisone 100 mg × 1d	6	94	4
Dexamethasone 4 mg × 1d	7	112	4
Cortisone 80 mg × 1d	6	96	4

TABLE 2. *Results of the Mortality Study Comparing Each Methylprednisolone Treatment Group with its own Controls*

	Methylprednisolone					
	5 mg bid × 2d		10 mg bid × 2d		20 mg × 1d	
	untreated	treated	untreated	treated	untreated	treated
Number of Rats	29	30	31	40	60	67
Deaths (%)	34.5	26.7	64.5	15.0	53.0	14.9
Average Time of Death hrs. ± S.E.	25.2 ± 3.1	44.8 ± 17.0	25.6 ± 2.5	73.2 ± 40.5	34.5 ± 3.9	24.5 ± 1.0

TABLE 3. *Results of the Mortality Study Comparing the Effect on Mortality of Four Corticosteroid Analogs With Their Own Untreated Controls*

	Methylprednisolone 20 mg × 1d		Hydrocortisone 100 mg × 1d		Dexamethasone 4 mg × 1d		Cortisone 80 mg × 1d	
	untreated	treated	untreated	treated	untreated	treated	untreated	treated
Number of Rats	60	67	46	40	25	39	41	40
Deaths (%)	53.0	14.9	30.4	40.0	68.0	23.1	34.1	32.9
Average Time of Death hrs. ± S.E.	34.5 ± 3.9	24.5 ± 1.0	32.0 ± 4.2	39.1 ± 4.1	46.6 ± 10.1	53.8 ± 17.3	32.1 ± 3.0	43.2 ± 16.3

single injection dosage schedule (Table 3), significant differences were noted. Dexamethasone 4 mg reduced the mortality to 23.1%, compared to 68.0% in the untreated controls, but no improvement was found with the administration of either hydrocortisone or cortisone.

Comparisons between expected and actual mortalities can be seen in Table 4. Methylprednisolone 5 mg bid × 2d resulted in a significant reduction in mortality to 77.4% of the expected ($P < 0.05$), and methylprednisolone 10 mg bid × 2d further lowered mortality to 23.3% of the expected ($P < 0.01$). A single injection of methylprednisolone, 20 mg, also resulted in a comparable improvement (28.1% of the expected).

The results of treatment using other corticosteroid analogs, reveals that only dexamethasone significantly reduced mortality ($P < 0.01$). There is, however, no significant difference between dexamethasone and methylprednisolone therapy. Cortisone treatment did not alter expected mortality, while hydrocortisone actually increased mortality to 131.6% ($P < 0.01$).

TABLE 4. *The Effect of the Six Different Treatment Groups on the Mortality Rate as Compared to the Expected Rate*

Treatment	% of Expected Late Deaths
Methylprednisolone 5 mg bid × 2d	77.4
Methylprednisolone 10 mg bid × 2d	23.3
Methylprednisolone 20 mg × 1d	28.1
Hydrocortisone 100 mg × 1d	131.6
Dexamethasone 4 mg × 1d	34.0
Cortisone 80 mg × 1d	96.5

Histologic examination of the lungs of rats, immediately following their removal from the chamber, revealed some interstitial edema, congestion, and inflammatory changes (Fig. 2). By 24 hours, interstitial edema was severe in the untreated rats, with marked congestion, atelectasis, and prominent inflammatory changes (Fig. 3). If the animal survived, the lungs essentially appeared normal two weeks post exposure (Fig. 4).

In marked contrast, rats receiving 5 mg of methylprednisolone, one hour post exposure, showed minimal changes at 4 hours post exposure (Fig. 5) and even less at 24 hours. Figure 6 shows an essentially normal lung at 24 hours post smoke inhalation, following the single administration of 20 mg of methylprednisolone.

Animals treated with dexamethasone showed a similar rapid improvement, but those treated with cortisone or hydrocortisone (Fig. 7) demonstrated pulmonary changes identical to the untreated controls.

Discussion

The results substantiate our previous work showing the feasibility of using the rat smoke inhalation model to evaluate the effectiveness of various treatments for smoke inhalation. Each treatment group, by necessity,

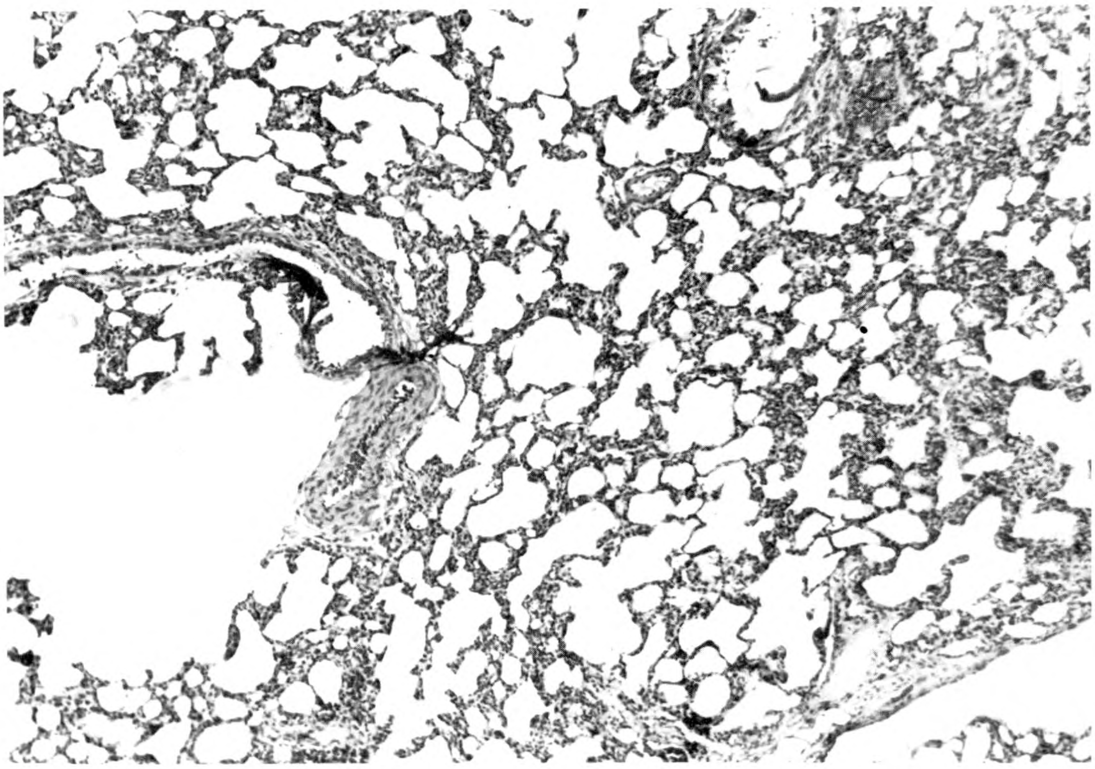

FIG. 2. Photomicrograph of a rat's lung immediately following exposure to white pine smoke (×180).

has its own untreated control animals within the same run to help eliminate run to run variation. This variation is probably related to the heterogenecity in the nature of the smoke produced by white pine wood, rather than biological variations or any defect in the smoke apparatus or experimental design. White pine wood is a naturally occurring polymer and thus, extremely variable in composition and compactness. Gas chromatography

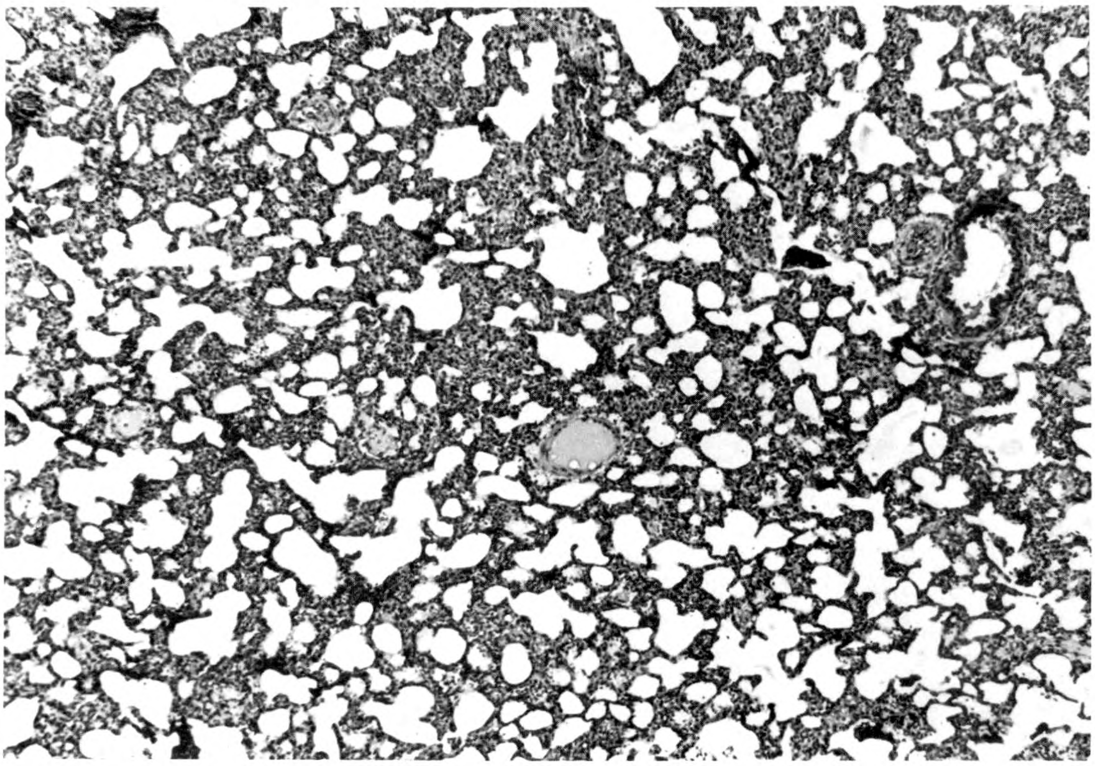

FIG. 3. Photomicrograph of a rat's lung 24 hours post exposure to white pine smoke (×180).

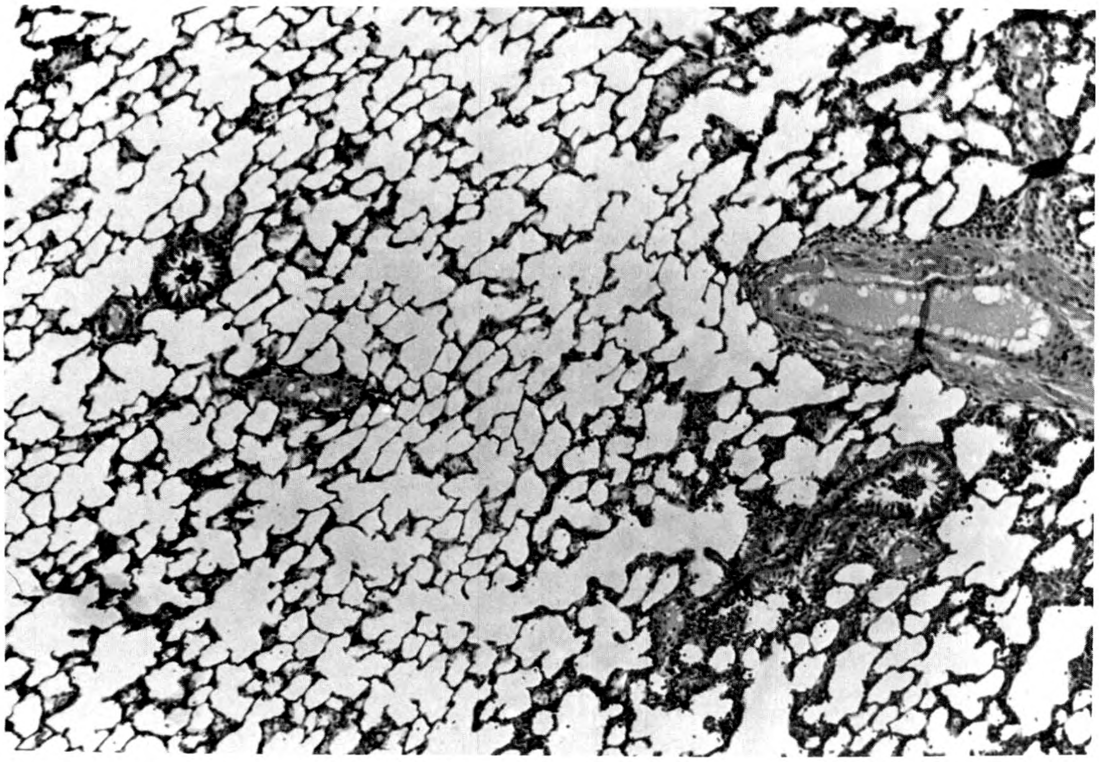

FIG. 4. Photomicrograph of a rat's lung two weeks post exposure to white pine smoke (×180).

confirms this variability in pyrolysates of white pine, although it does not identify the particular toxic agent involved.

It appears that inhalation of smoke produced by white pine wood results in a direct injury to the lung, such as suggested by the work of Zikria[14,15] which pointed to acrolien and aldehydes as the offending substances. This syndrome of late death may therefore

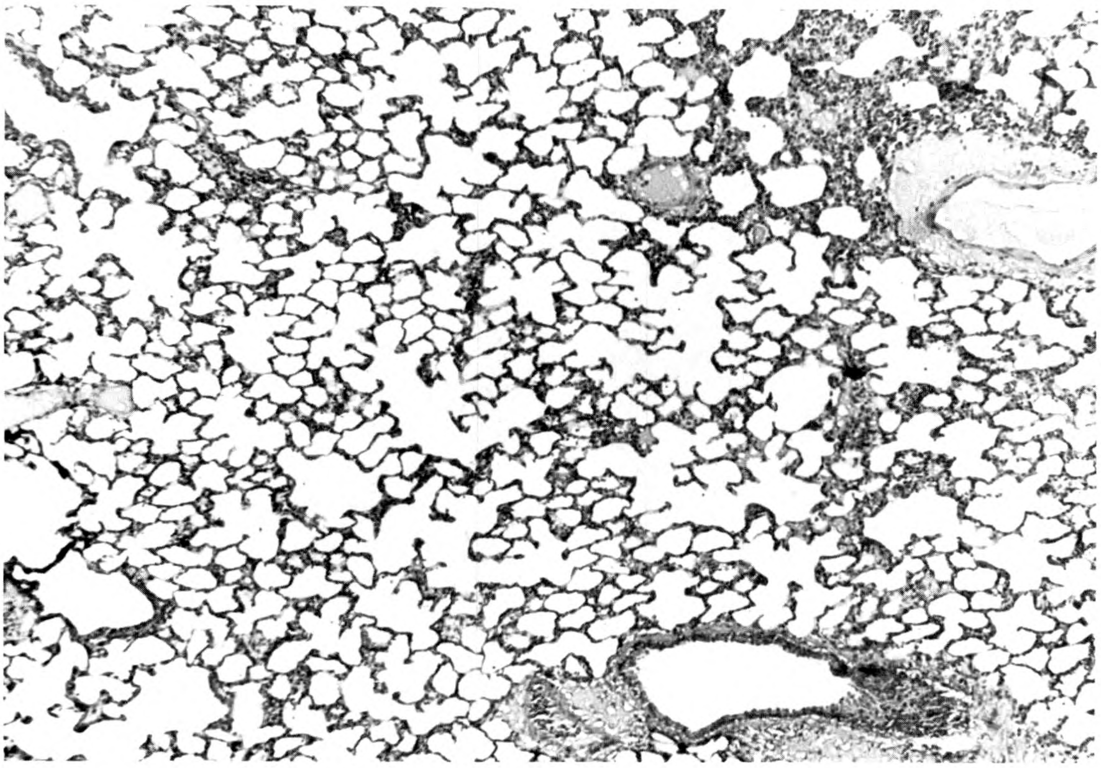

FIG. 5. Photomicrograph of the lung of a rat treated with Methylprednisolone, 5 mg bid × 2d, sacrificed 4 hours post white pine exposure (×180).

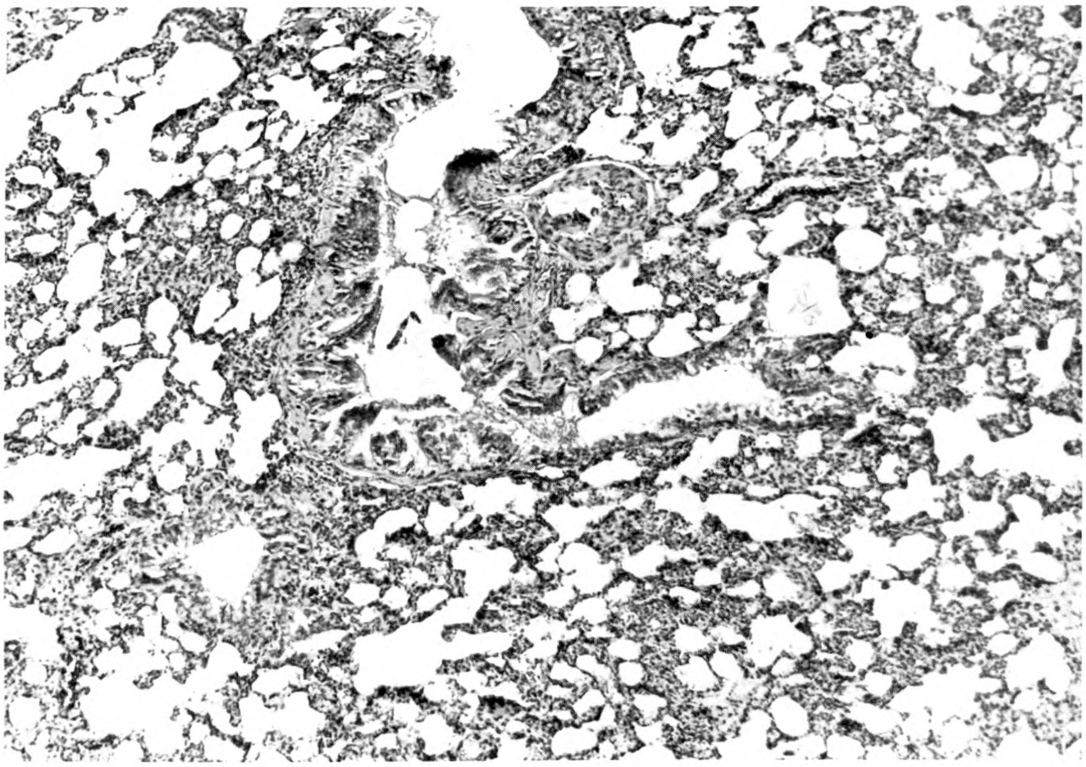

FIG. 6. Photomicrograph of the lung of a rat treated with Methylprednisolone, 20 mg × 1d, sacrificed 24 hours post white pine exposure (×180).

not occur when the smoke is produced from other materials. Indeed, we have reported in other studies that relatively few late deaths occur when animals are exposed to products of pyrolysis of synthetic polymers. Death, when it does occur, does not appear to be primarily due to direct injury to the lung.[3]

The fact that death following inhalation of white pine smoke is due to direct lung injury, suggests a

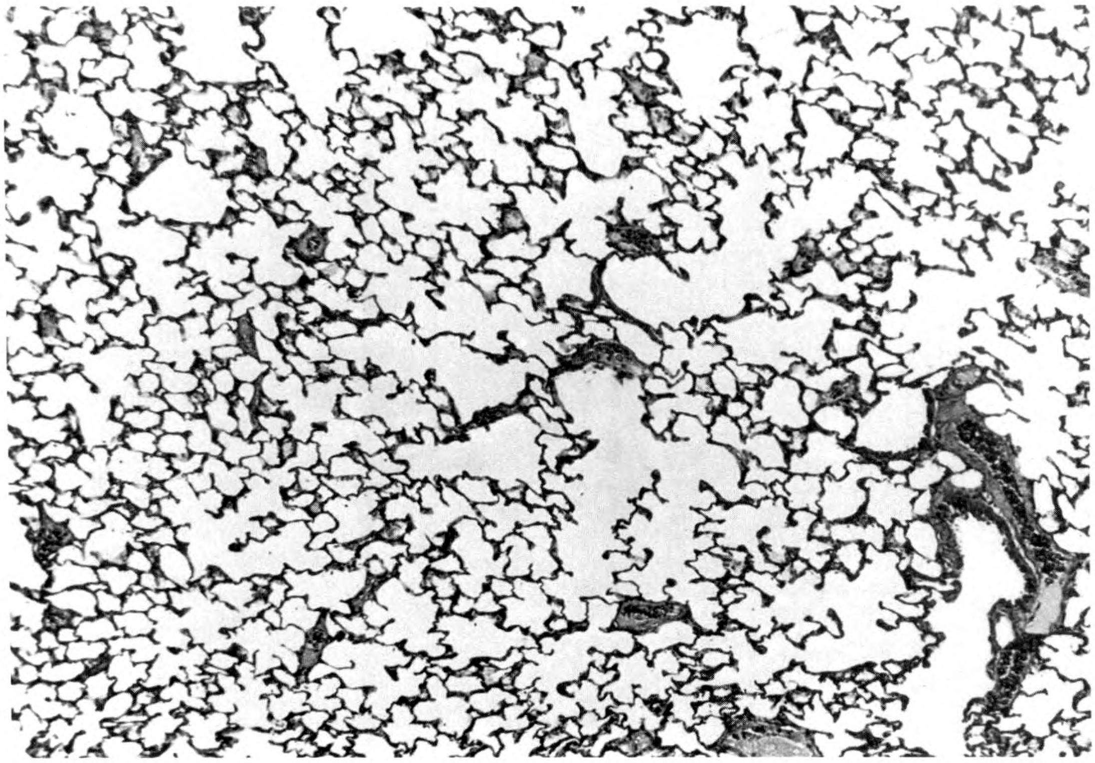

FIG. 7. Photomicrograph of a rat's lung treated with cortisone, 80 mg × 1d, sacrificed 24 hours post white pine exposure (×180).

possible mechanism of action of corticosteroid therapy. Steroids may increase survival by reducing the plasma leakage due to endothelial damage, a theory further substantiated by the marked reduction in interstitial edema expected shortly following smoke inhalation. It appears that those steroids with a high degree of glucocorticoid activity, i.e. methylprednisolone and dexamethasone, are the only analogs effective in treating smoke inhalation, in contrast to those with primarily mineralocorticoid activity.

Our results also indicate a definite dose response, even though the steroids were given on a non-pharmacologic basis, in doses considered massive (up to 100 mg/kg of methylprednisolone). It is not known whether higher doses of dexamethasone would be as effective as methylprednisolone, in which case the generally accepted anti-inflammatory equivalent dosages are not valid. However, even if those equivalents are invalid, hydrocortisone and cortisone appear to be ineffective.

In view of the massive doses indicated, further studies will be necessary to determine how many hours post exposure methylprednisolone may be administered and still be effective. This would be particularly significant in eliminating the possibility of incurring needless side effects, and expenses.

Evaluating the results obtained from altering the doses and dose schedules for methylprednisolone reveals that the single massive dose is almost as effective as smaller doses given on a two-day schedule. This is especially noteworthy when considering the side effects of steroid administration, particularly that of decreasing pulmonary bacterial resistance. Although even a single dose has been shown to eliminate most of the alveolar macrophages within 12 hours of administration, the resupply time for these essential cells has been reported to be between 36 and 48 hours. Hence, the normal defense mechanism, if interrupted, may be restored earlier following a single dose, as opposed to steroids given on a two-day schedule.

Use of the rat smoke model has shown steroids with glucocorticoid activity, such as methylprednisolone and dexamethasone, given in single massive doses, to be most effective in reducing mortality due to smoke inhalation. These results, when extrapolated to the clinical situation, may provide a basis for clinical investigations.

Acknowledgment

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Primary Carcinoma of the Appendix

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Primary adenocarcinoma of the appendix is rare and less than 200 cases are on record. The present material consisted of 20 cases collected from different hospitals. The cases are described in respect of sex and age-distribution, symptoms, treatment and prognosis. Of 7 patients with malignant mucocele, 6 subjected to appendectomy only, were still alive 5 years after the operation. Of 12 patients with colonic type of adenocarcinoma, 3 had been treated with appendectomy only. Of these, 2 were still alive 5 years after the operation. The remaining 9 patients had undergone right hemicolectomy. Only one of them was alive 5 years after the operation. A compilation of a further 39 cases garnered from the literature, however, showed that 60% had survived at least 5 years after right hemicolectomy, compared with 46% after appendectomy alone. Appendectomy alone is probably a sufficiently radical operation for malignant mucocele provided the tumor has not grown through the submucosa and that it is confined to the tip of the appendix. Right hemicolectomy is indicated for the colonic type of adenocarcinoma.

PRIMARY CARCINOMA of the appendix is rare. It was first described in 1882. The total number of cases since recorded is below 200.[8,14,16,20] Primary tumors of the appendix have long been classified as carcinoid, malignant mucocele and adenocarcinoma of the colonic type.

Collins (1955)[7] found adenocarcinoma in 41 of 50,000 appendices examined histopathologically. In 1970 41 cases of malignant tumor of the appendix were reported to the Swedish Cancer Registry. Of these tumors, 31 were carcinoids, 9 were adenocarcinomas and 1 was a malignant mucocele.[1]

The series of malignant tumors of the appendix on record consist mostly of only a few cases. This paper concerns an investigation of 20 cases of carcinoma of the appendix, the difficulties encountered in making a firm diagnosis and an endeavor to find the most suitable method of surgical treatment.

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Material

Between January 1959 and May 1970 a total of 20 patients had been treated at various hospitals in the district of Umeå, Sweden because of primary carcinoma of the appendix, exclusive of carcinoids. All of the cases had been confirmed histopathologically. The histological sections, which were still available for every patient were re-examined.

Seven (5 men and 2 women) patients had a malignant mucocele and 13 (9 men and 4 women) a colonic type of adenocarcinoma. The mean age of the patients with malignant mucocele at the time of the diagnosis was 46 years (range 35–57 years) and that of the remaining 13 patients 69 years (range 54–87 years). The age-distribution of the 13 patients with adenocarcinoma, including 165 garnered from the literature, is given in Fig. 1.

In one of our 20 cases the diagnosis had not been made before autopsy, while the other 19 patients were operated upon (Table 1). The preoperative diagnosis was acute appendicitis in 12, tumor of the right lower quadrant of the abdomen in 4, and ileus in the remaining 3 (Table 2). In none of the cases had the preoperative diagnosis been correct. In one patient (No. 5) with a colonic type of adenocarcinoma, the tumor had encroached upon the sigmoid and mesosigmoid. In another patient (No. 2) with the same type of carcinoma the tumor had extended over the anterior abdominal wall. One patient with malignant mucocele (No. 19) had pseudomyxoma peritonei.

In 4 of 7 patients the malignant mucocele was confined to the distal third of the appendix, compared with only 2 of 13 with adenocarcinoma of the colonic type.

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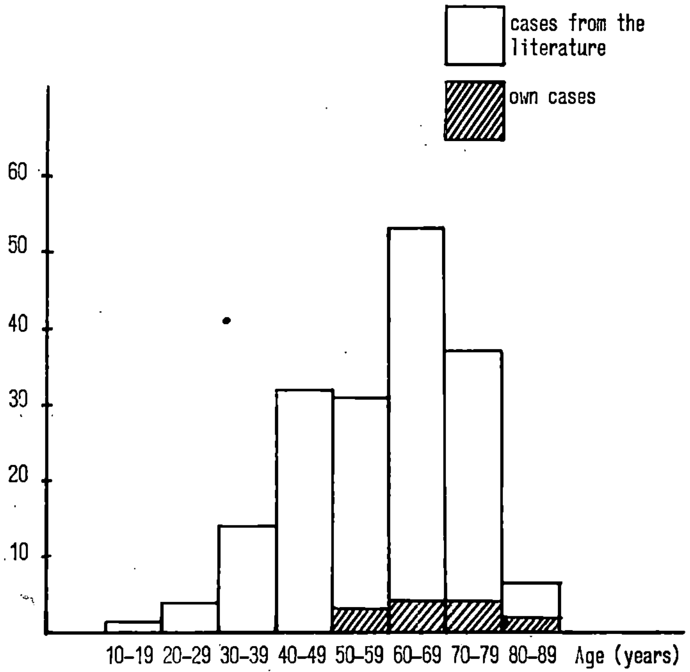

FIG. 1. Age distribution of 178 patients with adenocarcinoma of the colonic type of the appendix.

All the patients were followed until death or for at least 5 years.

Of 7 patients with malignant mucocele, 6 were treated with appendectomy only. All were still alive 5 years after the operation. One (No. 19) of these patients with rupture of the mucocele at the time of operation, however, died from a recurrence of carcinoma some 8 years after the operation (Table 3). The remaining patient with malignant mucocele was treated with right hemicolectomy, but died postoperatively from cardiac failure (Tables 1 and 3).

Twelve of the 13 patients with the colonic type of adenocarcinoma were operated upon. In 9 of these 12 cases the operation consisted of right hemicolectomy. One of these 9 patients died postoperatively from pulmonary embolism. Only 1 patient was alive 5 years after the operation. All the others had died from their basic disease (Table 4). Three of the 12 patients were treated with appendectomy alone. Of these, 1 had died from carcinoma. The other 2 were still alive with no signs of recurrence more than 5 years after the operation.

Case Reports

Two of the patients are of particular interest and are described in greater detail below.

Patient No. 1, a woman, was born in 1905. In 1935 she underwent cholecystectomy at which time an apparently healthy appendix was also removed. The appendix was not examined histopathologically. In 1955 she was subjected to gastric resection with gastrojejunostomy (Billroth II) because of a duodenal ulcer. Dumping symptoms developed. In 1962 the patient complained of diarrhea and pain in the right part of the abdomen. Roentgen examination of the colon at that time revealed nothing remarkable except for the invagination after appendectomy. The invagination was unchanged in size at subsequent examinations of the colon in 1962, 1963 and 1966. In March 1970 the patient's symptoms were more accentuated with pain in the right lower quadrant of the abdomen and alternating constipation and diarrhea. Roentgen examination of the colon then showed that the invagination had increased in size since the last roentgen examination. The patient was therefore operated upon in May 1970 with right hemicolectomy. Operation revealed a soft, polypoid, well defined tumor about 3 cm across at the site of the invagination. Histopathological examination revealed adenocarcinoma in the appendicular invagination without signs of spread. Also an inflammatory reaction was seen around the suture material after the earlier appendectomy. A typical Meckel's diverticulum was removed at the same time. Postoperative examination of the colon in 1970 revealed nothing remarkable. The patient is still alive without signs of a recurrence 5 years after the operation.

Patient No. 2, a man, was born in 1902. In 1922 he was operated upon because of perforated appendicitis with abscess. No details about the actual operation are known. In 1925 he was operated upon because of stone in the left ureter. He was admitted to hospital in 1959 because of loss of weight (10 kg) and of a fistula which he had had for about one month in the old appendectomy scar. A biopsy specimen of the fistula showed growth of mucus producing adenocarcinoma, which was probably a malignant mucocele. The patient was treated with right hemicolectomy and resection of the abdominal wall around the fistula. In the cecal pole, which was adherent to the anterior abdominal wall, was a tumor which histopathological examination showed to be a malignant mucocele. The patient died on the third day after the operation from acute cardiac failure. Autopsy revealed no residual tumor.

Discussion

According to Steinberg and Cohn,[23] adenocarcinomas of the appendix constitute 0.2–0.5% of all tumors of the gastrointestinal tract. The frequency with which primary adenocarcinoma has been found in operative specimens after appendectomy varies between 1 per 5,000[23] and 1 per 30,000.[25] In Sweden the frequency has been calculated as 1 per 1,500.[1] The diagnosis is most often not made before routine histopathological examination of the appendix. If only some of appendices removed are examined histopathologically, the frequency of carcinoma of the appendix will be underestimated.

Uihlein and McDonald[24] distinguished three types of primary tumors of the appendix: 1) Carcinoma of the carcinoid type; 2) Carcinoma of the cystic type producing pseudomyxoma peritonei; 3) Adenocarcinoma of the colonic type.

The carcinoids are the most common and constitute up to 90% of all primary tumors of the appendix.[22] Histologically, a malignant mucocele is regarded as a well differentiated adenocarcinoma.[11,13,15] Since the malignant mucocele differs by a therapeutic and prognostic point of view from the colonic type of adenocarcinoma, these patients are accounted for separately in the present report.

Malignant mucocele rarely spreads lympho- or hematogenically.[10,15,19] Only rarely has such spread been reported.[3,5,11,21] The absence of lymphogenic spread suggests that appendectomy alone is a sufficiently radical operation.

In 7 patients with malignant mucocele in the present

TABLE 1. *Data on 20 Patients With Primary Carcinoma of the Appendix*

Patient No.	Sex, Age	Present Complaints and Findings	Operative Findings	Treatment	Microscopic Findings*	Results
1	F, 65	See Case report	Cecal tumor with a diameter of 3 cm	Right hemicolectomy	A	No recurrence (5 yrs)
2	M, 57	See Case report	Big cecal tumor adherent to abdominal wall	Right hemicolectomy and abdominal wall resection	M	Died of cardiac failure (3 days)
3	F, 56	Melena Right lower quadrant mass. Ovarian tumor?	Appendiceal tumor with a diameter of 10 cm	Appendectomy	M	No recurrence (9 yrs)
4	F, 54	Typical for acute appendicitis	Appendiceal tumor with a diameter of 7 cm	Appendectomy Radiotherapy	M	No recurrence (11 yrs)
5	F, 82	Constipation. Colicly abdominal pain. X-ray: Ileus	Appendiceal adenocarcinoma with metastases to sigmoid and mesentery	Appendectomy and resection of sigmoid	A	Died of metastases (6 mon)
6	M, 45	Typical for acute appendicitis	Appendicitis with perforation	Appendectomy	M	No recurrence (6 yrs)
7	M, 44	Typical for acute appendicitis	Appendiceal tumor with a diameter of 3 cm	Appendectomy	M	No recurrence (5 yrs)
8	M, 72	Ascites	Autopsy: Appendiceal adenocarcinoma with carcinosis peritonei	No operation	A	—
9	F, 67	Typical for acute appendicitis	Appendiceal abscess	1. Appendectomy 2. Right hemicolectomy	A	Died of metastases (1 yr, 7 mon)
10	M, 57	Typical for acute appendicitis	Appendiceal abscess	1. Drainage 2. Appendectomy	A	No recurrence (5 yrs)
11	M, 69	Typical for acute appendicitis	Appendiceal tumor with a diameter of 10 cm	Right hemicolectomy	A	Died of metastases (1 yr, 11 mon)
12	F, 72	Colicly abdominal pain, vomiting, X-ray: Ileus	Appendiceal tumor with a diameter of 7 cm	Right hemicolectomy	A	Died of pulmonary embolism (2 wks)
13	M, 80	Typical for acute appendicitis	Appendiceal tumor with a diameter of 2 cm	1. Appendectomy 2. Right hemicolectomy	A	Died of metastases (8 mon)
14	M, 33	Typical for acute appendicitis	Appendicitis with perforation	Appendectomy	M	No recurrence (11 yrs)
15	M, 72	Typical for acute appendicitis	Appendiceal tumor with a diameter of 2 cm	1. Appendectomy 2. Right hemicolectomy	A	Died of metastases (6 mon)
16	M, 77	Colicly abdominal pain X-ray: Subileus	Appendiceal abscess	1. Appendectomy 2. Right hemicolectomy	A	Died of metastases (6 mon)
17	M, 55	Right lower quadrant mass	Appendiceal tumor	Appendectomy	A	No recurrence (5 yrs)
18	M, 67	Typical for acute appendicitis	Appendiceal abscess	1. Appendectomy 2. Right hemicolectomy	A	Died of metastases (2 yrs)
19	M, 53	Typical for acute appendicitis	Appendiceal tumor with perforation and pseudomyxoma peritonei	Appendectomy Radiotherapy	M	Died of metastases (8 yrs, 2 mon)
20	M, 54	Typical for acute appendicitis	Appendicitis	Appendectomy	A	Died of cardiac infarction (1 yr. 10 mon)

* A: adenocarcinoma of the colonic type. M: malignant mucocele.

material right hemicolectomy was done in one, who subsequently died from acute cardiac failure. The remaining 6 patients were subjected to appendectomy alone and all of them were still alive 5 years after the operation. One of them with a perforated mucocele, however, died from a recurrence of the carcinoma 8 years after appendectomy. In another patient there was perforation of the mucocele. That patient has been free from recurrences for

TABLE 2. *Preoperative Diagnosis in 19 Cases*

Acute appendicitis	12
Ileus	3
Carcinoma of the cecum	2
Right lower quadrant mass	1
Ovarian tumor	1

6 years after the operation, which consisted of appendectomy alone. Otto et al.[20] reported that perforation of the mucocele has not any notable effect on the prognosis. Edmondson and Hobbs,[9] however, recommend right hemicolectomy for perforated malignant mucocele. But, judging from the present material, appendectomy alone is sufficient for malignant mucocele confined to the tip of the appendix and not invading the submucosa.

The mean age of the patients with malignant mucocele in the present material was 46 years, compared with 69 years for patients with colonic type of adenocarcinoma. Lower mean ages for malignant mucocele than for colonic type of adenocarcinoma have also been reported by other authors.[19,29] Both groups of our patients were older than those published.

Like Sieracki and Tesluk,[22] but unlike Otto et al.[20] we found both groups of malignant tumors of the appendix to be more common among males.

The colonic type of adenocarcinoma is often localized to the base of the appendix.[18] In our material only 2 of 13 such carcinomas were confined to the distal third. The colonic type of adenocarcinoma spreads lymphogeneously or hematogeneously, besides which it penetrates the wall of the appendix.

The main lymphatic and venous drainage of the appendix is essentially that of the cecum and terminal ileum. Thus, almost any node of the entire upper or lower ileocolic chain may be a primary drainage area for the appendix. Once a primary lesion is found in the appendix, the drainage areas of the anterior surface of the third portion of the duodenum and above the origin of the ileocolic artery should be checked for gross involvement.[15]

Because of the mode of spread of adenocarcinoma right hemicolectomy should be performed in all cases of the colonic type of adenocarcinoma.[12,23] Hesketh[12] studied 95 patients. Adequate followup data were, however, available for only 50 of these patients, who had been collected from a large number of publications. In those patients operated upon by appendectomy alone, the 5-year survival rate was 20%, compared with 63% in the group subjected to right hemicolectomy. We have collected 39 cases of primary adenocarcinoma of the appendix of the colonic type from the literature between the years 1956–1973.[9,10,14,17,20] Together with 12 personal cases the material consisted of 51 cases. Of 26 patients treated with appendectomy alone, 12 (46%) were still alive 5 years after the operation, compared with 15 (60%) of 25 subjected to right hemicolectomy. Right hemicolectomy should always be performed for carcinoma of the appendix of the colonic type.

TABLE 3. *Seven Cases of Malignant Mucocele of the Appendix*

Operative Procedure	No. of Cases	Primary Deaths	5-year Survival
Appendectomy	6	0	6
Right Hemicolectomy	1	1	0

TABLE 4. *Twelve Cases of the Colonic Type of Adenocarcinoma of the Appendix*

Operative Procedure	No. of Cases	Primary Deaths	5-year Survival
Right Hemicolectomy	9	1	1
Appendectomy	3	0	2

In one (No. 1) patient, carcinoma of the appendix developed in an invaginated stump of the appendix. At repeated roentgen examination of the colon during a 4 year period 27 years after appendectomy, the size of the invagination and its appearance were still unchanged. After a further 4 years examination because of abdominal pain and melena the invagination was found to have increased in size and the patient was operated upon. The possibility of carcinoma in the appendicular invagination, which increases in size should be borne in mind. Also occult blood in the stools together with an appendicular invagination, when no other source of bleeding can be found, is reason enough to suspect carcinoma of the invagination.

In 8% of the cases the appendicular invagination caused a filling defect in the cecum at roentgen examination of the colon.[2] Polyps in the cecum,[30] like foreign body granuloma in the stump of the appendix,[28] can produce a similar picture. Carcinoma in the appendicular invagination has been described by Vidal.[26] Such an invagination should also be distinguished from lipomatosis of the ileocecal valve.[4] Roentgenologically, an appendicular invagination cannot be distinguished with certainty from a cecal polyp.[30]

A late complication of appendicular invagination is inflammation with abscess-formation.[6,27] This complication may occur in those cases where appendectomy has been incomplete. This may occur if the appendix is removed en passant in association with other abdominal operations with a less suitable surgical technique for appendectomy and less suitable incision resulting in poor access to the base of the appendix. In our case the adenocarcinoma of the appendix occurred in an appendicular stump after appendectomy en passant at cholecystectomy.

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Evaluation of Catheter Placement in the Treatment of Venous Air Embolism

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Venous air embolism is a potential complication of many surgical, therapeutic, and diagnostic procedures. Aspiration of air via a catheter placed in the superior vena cava or right atrium or placed in the pulmonary outflow tract and pulled through the right heart chambers has been advocated for the treatment of venous air embolism. In this study, three catheter positions were analyzed to determine which was best for removal of gas after induction of massive venous air embolism in dogs. In 18 dogs, 9 of which were suspended by their forelegs to simulate the sitting position used in posterior fossa exploration and 9 of which were supine, a Swan-Ganz catheter was placed in the right atrium, right ventricle, or pulmonary artery. A measured amount of air was injected into the left jugular vein and syringe aspiration of the air was attempted through the catheter. In the group with the catheter in the pulmonary artery, aspiration was continuous while the catheter was withdrawn through the right heart chambers. The amount of air aspirated varied widely among the three catheter positions, and no one catheter position proved superior to the other two.

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VENOUS AIR EMBOLISM, although relatively infrequent, is a potentially catastrophic complication of many surgical, therapeutic and diagnostic procedures. In a survey involving over 60,000 operations, Dornette and Orth[6] reported that fatal venous air embolism was responsible for two of the 108 reported deaths. Documented causes of venous air embolism include the use of air for radiologic contrast studies,[9,10,12,13,15,25] injection of air into the urogenital tract,[4,14,16,18] improper technique while giving intravenous fluids or taking blood donations,[3,24,26,27] operations on the head and neck,[1,29] induction of pneumoperitoneum,[2,5] and the use of methylmethacrylate in total hip replacement.[23] However, venous air embolism is probably most frequently observed during neurosurgical procedures done in the sitting patient, particularly occipital craniotomy for exploration of the posterior fossa.[11] Although Michenfelder et al.[21] reported an incidence of venous air embolism of only 2.6% (11 of 418 patients) in occipital craniectomies, Marshall[17] reported an incidence of 15% (5 of 34 patients) and Tateishi[28] an incidence of 40% (8 of 20 patients). The high incidence in such procedures is due to the increased likelihood of a noncollapsible venous channel (diploic vein or dural sinus) being opened which could then aspirate air in the presence of negative venous pressure.

Many procedures have been recommended for the treatment of air embolism most of which are directed at elevating venous pressure and removing intracardiac air. Venous pressure in the head can be raised by applying continuous positive pressure breathing and internal jugular vein compression.[19] When the venous pressure is raised, further entry of air is prevented, and the surgeon may be better able to locate the open venous channel. Other measures recommended include placing the patient in the left lateral decubitus position to dislodge the bubble of air from the right ventricular outflow tract,[7] administering oxygen and vasopressors, and initiating closed chest cardiac massage.[8]

In 1966, Michenfelder et al.[21] advocated the aspiration of air from the heart via polyethylene catheters placed in the superior vena cava or the right atrium. In 1975, Munson et al.[22] stated that bubbles of embolized gas in pulmonary arterioles can adversely affect pulmonary artery pressure and the end-tidal carbon dioxide concentration long before signs of intracardiac air appear.

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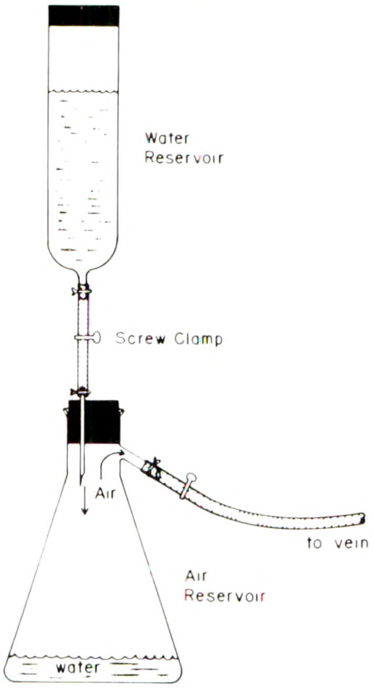

FIG. 1. Apparatus for injecting a measured amount of air to create embolus.

Such bubbles are inaccessible to conventional central venous lines. They suggested using a triple-lumen Swan-Ganz catheter for the aspiration of gas from the pulmonary outflow tract, and the CVP port of the Swan-Ganz catheter for removal of air from the right ventricle and right atrium. Alternatively, they suggested that pulmonary arterial, right ventricular and right atrial air could be evacuated effectively by continuous aspiration as the Swan-Ganz catheter was withdrawn through these chambers. However, in the episode of venous air embolism described in their paper, no gas could be aspirated from the pulmonary artery Swan-Ganz catheter.

The present study was designed to determine the best catheter position for the removal of gas after induced massive venous air embolism.

Method

Eighteen beagle dogs weighing from 6.8 to 12.5 kg were divided into two groups of 9 dogs each. Dogs in Group A were placed supine; dogs in Group B were suspended by their forelegs to simulate the sitting position used in exploration of the posterior fossa. Each dog was anesthetized with sodium pentobarbital, intubated, and placed on a volume respirator delivering 100% oxygen and a tidal volume of 12 cc/kg. The respiratory frequency was set at a rate sufficient to maintain the P_{CO_2} at 40 ± 5 torr. Catheters were inserted in the left femoral artery and vein and attached to a Grass Model 5 polygraph for monitoring arterial and central venous pressures. The left external jugular vein was exposed and cannulated with a large intravenous catheter attached to a water displacement apparatus for injection of precise volumes of air (Fig. 1). The right external jugular vein was ligated and cannulated with a 5 or 7 Fr. Swan-Ganz catheter which was then advanced to one of three aspiration positions, the location of the catheter tip being determined by monitoring of the pressure wave form. In each group the catheter was placed in the right atrium in three dogs, in the right ventricle in three dogs and in the pulmonary artery in three dogs. The Swan-Ganz catheter was connected to a syringe and to a second water displacement apparatus (Fig. 2).

A volume of 8 cc/kg of air was injected through the left external jugular vein over a 10- to 20-second interval. Syringe aspiration through the Swan-Ganz catheter was started within seconds after the air injection was completed. In the group with pulmonary artery catheter placement, the catheter was slowly withdrawn through the right heart chambers while aspiration continued. The amount of air recovered, as measured with the second water displacement apparatus, was recorded. Central venous pressures, arterial pressures and electrocardiography were monitored throughout the experiment.

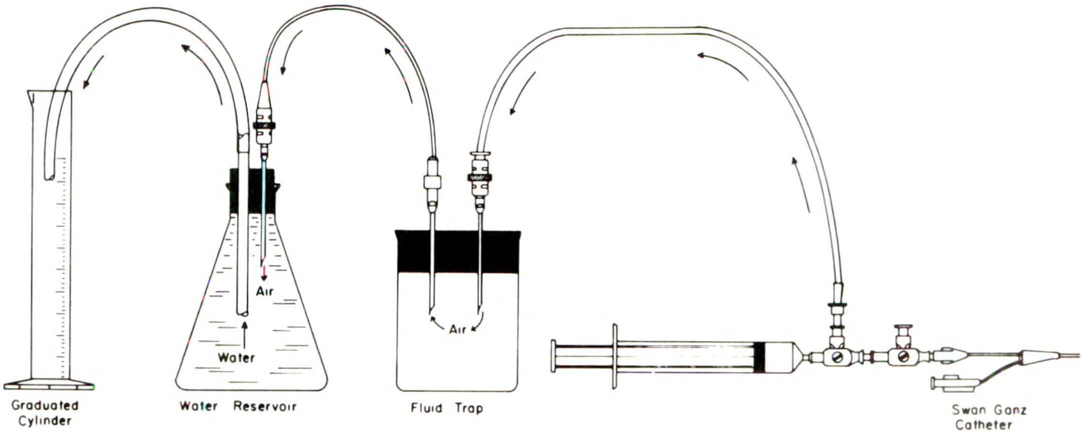

FIG. 2. Apparatus for measuring amount of air aspirated through catheter.

TABLE 1. *Volume of Air Recovered by Catheter Aspiration per Dog following Induced Massive Venous Air Embolism in Nine Dogs in Supine Position*

Maneuver	Volume Air Injected (8 cc/Kg)	Volume Air Retrieved By Syringe Aspiration	$\frac{\text{Volume Retrieved}}{\text{Volume Injected}} \times 100$	Survivors
Pulmonary Artery Aspiration with Subsequent Retrograde Sweep Back (3 dogs)	56 cc	12 cc	21%	–
	72 cc	37 cc	51%	+
	85.6 cc	15 cc	17%	+
Right Ventricular Aspiration (3 dogs)	85.6 cc	22 cc	26%	–
	85.6 cc	14 cc	16%	–
	84 cc	37 cc	44%	–
Right Atrial Aspiration (3 dogs)	80 cc	14 cc	17%	–
	70.4 cc	10 cc	14%	+
	70.4 cc	19 cc	27%	–

Death was defined as a blood pressure of 0 mmHg for at least ten minutes. Autopsy was done on all dogs.

Results

The systemic arterial pressure fell and central venous pressure rose dramatically in all dogs after air infusion. In all but three dogs the air embolus proved fatal, with blood pressure declining to zero within minutes. In the three surviving dogs, both blood pressure and central venous pressure returned to normal values over 45 to 60 minutes.

The results of aspiration with the Swan-Ganz catheter in various positions are shown in Tables 1 and 2. All three surviving dogs were in Group A, that is, dogs in the supine position. In two of the survivors, the catheter tip had been placed in the pulmonary artery and withdrawn slowly during aspiration. In the other survivor, the catheter tip had been located in the right atrium. Postmortem examination of the nonsurvivors revealed air in the right ventricle, the right atrium, the superior and inferior vena cavae, the intercostal veins and the coronary veins. The right ventricle frequently contained a foamy clot. In dogs in which the catheter had not been withdrawn during the experiment, the position of the catheter tip proved to be correctly placed in the atrium or the ventricle.

Discussion

The results of this study indicate that, in beagles, aspiration through a Swan-Ganz catheter placed in the right atrium, right ventricle, or pulled back through those chambers from the pulmonary artery is an unreliable means of treating massive venous air embolism. Both the absolute volume of air aspirated and the volume of air aspirated expressed as a percentage of that injected varied widely for each catheter placement. Although all three surviving dogs were in Group A (supine) and two of the three did have pulmonary artery pull-through aspiration, the reason for their survival is not apparent from the data. We believe that the survival of these dogs was fortuitous, and that no one catheter position was superior to the other two in this study.

While it has become routine in many hospitals to place catheters in the right atrium or superior vena cava before the start of surgical procedures that are likely to be complicated by air embolism, experimental evidence supporting their use is lacking. In our study—the only one we know of that has evaluated the efficacy of right

TABLE 2. *Volume of Air Recovered by Catheter Aspiration per Dog following Induced Massive Venous Air Embolism in Nine Dogs in Sitting Position*

Maneuver	Volume Air Injected (8 cc/Kg)	Volume Air Retrieved By Syringe Aspiration	$\frac{\text{Volume Retrieved}}{\text{Volume Injected}} \times 100$	Survivors
Pulmonary Artery Aspiration with Subsequent Retrograde Sweep Back (3 dogs)	87.2 cc	34 cc	39%	–
	76 cc	40 cc	53%	–
	61.8 cc	11 cc	16%	–
Right Ventricular Aspiration (3 dogs)	74 cc	34 cc	46%	–
	72 cc	20 cc	28%	–
	84 cc	8 cc	9%	–
Right Atrial Aspiration (3 dogs)	100 cc	23 cc	23%	–
	54.4 cc	10 cc	18%	–
	72 cc	10 cc	14%	–

atrial catheters in the treatment of an air embolus of known volume—the results of such catheter placement proved inconsistent at best. There is also clinical evidence of the variable effectiveness of right atrial catheters. In 1969, Michenfelder et al.[20] reported 23 episodes of air embolism in patients in whom a right atrial or superior vena cava catheter had been used. In 8 of the 23 episodes the volume of air aspirated was between 10 ml and 400 ml, but in 15 of the episodes the volume of air aspirated was less than 10 ml and was probably insufficient to have contributed to the treatment.

Our study did not confirm the suggestion by Munson et al.[22] that aspiration during withdrawal of the Swan-Ganz catheter from the pulmonary artery through the right heart chambers has any advantage over conventional right atrial catheter placement.

The established practice of placing a catheter in the right atrium before the start of a surgical procedure accompanied by a high risk of air embolism will probably be continued, since it is sometimes life-saving and often of diagnostic value. However, the surgeon and anesthesiologist should be aware of the unreliability of this procedure as a consistent means of treating air embolism. On the basis of this study, we do not believe that placement of a Swan-Ganz catheter in the ventricle or pulmonary artery for such a purpose is merited unless further study can indicate its effectiveness.

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The Modified Bovine Heterograft in Vascular Access for Chronic Hemodialysis

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The results of 100 modified bovine heterografts constructed in 93 patients for subcutaneous arteriovenous fistulas for chronic hemodialysis have been reviewed. Fifty-seven patients had the bovine heterograft inserted as the primary method of vascular access. Twenty-eight patients had complications consisting of graft thrombosis and stenosis, graft infection, and hemorrhage that required additional surgical procedures. Three patients with diabetes mellitus developed ischemia of the hand. Fourteen patients have died but none of the deaths could be attributable to the use of the bovine heterograft. In our experience the modified bovine heterograft has enjoyed a higher patient acceptance as compared to other methods of vascular access for hemodialysis. The chief advantage of the bovine graft has been the ability to use the graft in any patient as a means of immediate dialysis.

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THE CAPABILITY of repeated access to the peripheral circulation is a critical factor in the successful management of patients with end-stage renal disease who undergo chronic hemodialysis. The silastic arteriovenous cannula was a major breakthrough in this regard.[6] Frequency of thrombosis and infection, however, have prompted the use of subcutaneous arteriovenous fistulas.[1] We have reported our experience with 25 patients in whom the modified bovine heterograft was used in the construction of subcutaneous arteriovenous fistulas.[3] Through the continued use of the modified heterograft, certain peculiarities of this prosthesis have become aparent, and it is now possible to make specific recommendations for its use in the patient with end-stage renal disease.

Materials and Methods

From May 1973 through March 1975, 93 patients at Good Samaritan Hospital Kidney Center and Maricopa County General Hospital Dialysis Unit, Phoenix, Arizona, have been dialyzed using the modified bovine heterograft (Table 1). Fifty of these patients were male; 43 female. The age range for this group was 16 years to 74 years, with a mean age of 44 years. One-hundred arteriovenous fistulas have been created, using the modified bovine heterograft, according to techniques of graft preparation and insertion described in an earlier report.[3] Fifty-four fistulas were straight forearm grafts, and 24 were loop forearm grafts. Straight thigh fistulas were placed in 18 patients, 3 patients had a loop thigh graft, and one patient had an axillo-axillary graft. The period of observation has ranged from four to 102 weeks. This excludes 3 patients who refused dialysis, 3, 5 and 9 weeks postoperatively. Fifty-seven patients had bovine arteriovenous fistulas constructed as the first method of vascular access. The remaining patients had had arteriovenous cannulas, radiocephalic arteriovenous fistulas, or saphenous vein reroutings prior to the construction of the modified bovine heterograft arteriovenous fistula. General anesthesia was administered in 72 cases, local anesthesia and sedation in 24 cases, and 4 patients had regional block.

Results

Satisfactory results have been obtained using the modified bovine heterograft for the construction of arteriovenous fistulas. In 45 cases there were no complications, 28 patients had complications requiring surgical intervention with the remaining patients experiencing complications not requiring additional surgery.

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Non-operative complications. Most patients developed some degree of postoperative localized edema in operated extremities, and 10 patients had persistent swelling from 2 to 4 months following surgery. Nine of these patients had received straight thigh fistulas, and one had a loop forearm fistula. The swelling has not been incapacitating in any case, but it has resulted in minimal separation of incisional lines, with subsequent delay in wound healing and difficulty in graft palpation. Since electromagnetic flow rates of forearm and thigh fistulas have averaged 440 cc per minute and 880 cc per minute, repsectively, it seems valid to assume that the edema seen commonly in thigh fistulas is the result of a higher venous pressure. In most instances, limited ambulation, elevation of the affected extremity, and precise elastic support has helped to control swelling.

Localized skin necrosis of the incision over the radial artery occurred in one patient with a straight forearm graft and was the direct result of extensive tissue undermining. Local wound care resulted in healing without infection of the graft.

Three patients with straight thigh fistulas developed bleeding in the subcutaneous tunnel but did not require reoperation. This bleeding may have resulted from inaccurately applied compression after removal of the dialysis needles. Application of pressure over the site of skin perforation may not cause tamponade at the graft site because the point of graft puncture is often different from the skin puncture site. When this is the case, bleeding may continue into the tract alongside the graft. Since skin and subcutaneous tissue are thicker in the thigh, more bleeding complications may be expected with thigh fistulas.

One patient in our series developed an aneurysm in the midportion of the graft secondary to multiple needle punctures in one area of the graft. The aneurysm slowly enlarged over a period of 6 weeks but has remained stable during the past 8 months. There has been no sign of further enlargement, skin erosion, infection, or embolization. To avoid aneurysm formation from repeated needle punctures in one location, it is necessary to use numerous puncture sites along the full length of the graft, sparing 2 cm nearest each anastomosis. Also single-needle dialysis may decrease the number of true or false aneurysms associated with repeated cannulations.

Fourteen of the patients in the series have diabetes mellitus. Straight forearm arteriovenous fistulas were constructed in 4 cases, and the other 10 diabetic patients had loop forearm fistulas. Patients with diabetes mellitus have significant small-artery atherosclerosis, and the creation of an arteriovenous fistula by graft interposition appears to hasten the progression of atherosclerotic occlusion.[4] Gradual occlusion of the proximal radial artery over a 10-month period occurred in one diabetic patient following placement of a straight forearm fistula. Because of retrograde flow through the distal radial artery, via the palmar arch and ulnar artery, the graft remained patent (Fig. 1). However, progressive decrease in flow through the graft necessitated construction of a loop forearm fistula in the contralateral arm. With our experience with this one case, it appeared that ischemia may be avoided by constructing loop forearm fistulas in all diabetic patients. However, this was not the case and three patients with diabetes mellitus developed pain, paresthesia, and coolness of the ipsilateral hand following placement of loop forearm fistulas. Progression of these ischemic symptoms has not occurred. All 3 patients had adequate preoperative radial and ulnar artery perfusion of the hand.

TABLE 1. *Operative Experience with Bovine Arterial Grafts*

Number of Patients	93
Male	50
Female	43
Number of Grafts	100
Forearm, straight	54
Forearm, loop	24
Thigh, straight	18
Thigh, loop	3
Axillo-axillary	1
Age Distribution	
10–19	8
20–29	14
30–39	12
40–49	16
50–59	30
60–69	9
70–79	4

Operative complications (Table 2). In our series, reoperation was necessary to reverse such complications as graft thrombosis, graft infection with false aneurysm formation, hemorrhage and bovine graft stenosis. For purposes of discussion, we have arbitrarily classified thrombosis according to the time of its occurrence, i.e., within one week of operation (early), or after one week (late).

Four patients had early thrombosis of the graft, and in two of these cases, exploration at the time of reoperation did not reveal a specific cause for thrombosis. Following thrombectomy, both bovine heterografts have remained patent for 9 and 14 months, respectively. In a third patient, a loop forearm fistula thrombosed within 12 hours following surgery, and at reoperation kinking of the mid-portion of the graft was found (Fig. 2). After resection and anastomosis, the graft has remained patent. Thrombosis of a straight forearm fistula in another patient occurred during dialysis 3 days following graft placement. Thrombosis appeared to be secondary to embolization from arterial line clotting within the dialysis machine.

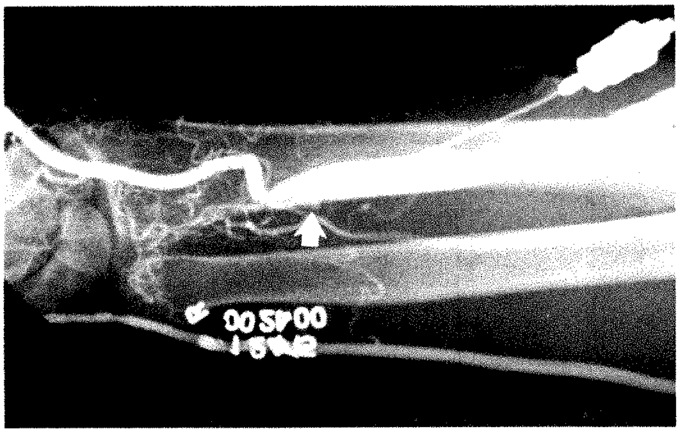

FIG. 1. Graft patency maintained by distal radial artery with occlusion of the proximal radial artery (arrow).

At reoperation, no mechanical basis for the thrombus was found, and four months following thrombectomy, the graft remains patent.

Temporary low flow states were documented prior to late thrombosis in two patients. In a third case, no explanation for thrombosis was found. Following thrombectomy all 3 grafts have remained patent at 5, 7, and 11 months, respectively. Proliferation of pseudo-intimal fibrous tissue resulted in the occlusion of 6 grafts 4 to 15 months after insertion. All cases have involved the venous anastomosis, which leads us to the conclusion that the increased turbulence from retrograde flow in the veins must play a role in the genesis of obstructions of this type. Because of occlusion at the saphenofemoral junction in one thigh fistula, the common femoral vein is now used as a venous outflow track. In one case, however, stenosis of the bovine graft developed in spite of the fact that the venous anastomosis was made at the common femoral vein (Fig. 3). One variation in technique which may improve flow characteristics is a longer venotomy, which may reduce turbulence. Histologic studies of resected specimens have consistently shown proliferation of fibrous tissue and hyalinization throughout the length of the graft and particularly prevalent near the venous anastomosis. Pseudo-intimal fibrous proliferation with resultant graft stenosis can be anticipated when there is a consistent rise in venous resistance during dialysis. This phenomenon has been noted in 6 patients in whom contrast studies of the bovine graft disclosed significant venous stenosis. In all 6 cases, revision of the venous anastomosis was performed before the thrombosis occurred. In such cases, our procedure has been to remove the pseudo-intimal fibrous tissue by endarterectomy, followed, when necessary, by bovine, vein or Dacron patch-graft angioplasty (Fig. 4).

TABLE 2. *Operative Complications*

	No. of Patients	Bleeding	Thromboses Early	Thromboses Late	Infection	Bovine Graft Stenosis
Straight forearm graft	54	—	3	9	1	4
Loop forearm graft	24	—	1	1	2	—
Straight thigh graft	18	2	—	2	—	2
Loop thigh graft	3	—	—	—	—	—
Axillo-axillary graft	1	—	—	—	—	—

Infection of the modified bovine heterograft has developed in three patients, one of whom was clawed by a pet cat. This injury resulted in graft puncture and subsequent infection, false aneurysm formation, and hemorrhage. Partial removal of this graft has been necessary. In the other two cases, infection occurred at 6 and 51 weeks, respectively. The grafts were surgically removed, and modified bovine heterografts were placed in new locations in both of these patients. This low incidence of infection may be attributable to our technique of preparing the extremity prior to cannulation for dialysis with routine surgical scrub and mask and glove precautions.

Postoperative bleeding of sufficient magnitude to require reoperation occurred in two patients early in the series. Both had straight thigh fistulas, and suture ligation of a posterior wall puncture was necessary to control the bleeding in both instances. Since then this complication has not occurred, partly because of increased experience with cannulation, but more im-

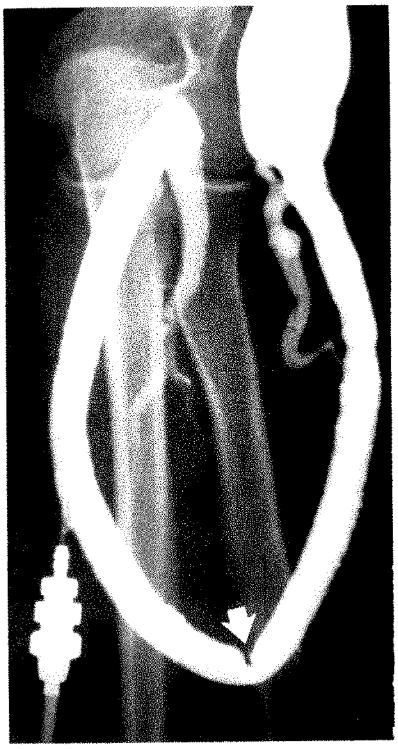

FIG. 2. Kinking of bovine heterograft placed in the forearm as a loop fistula.

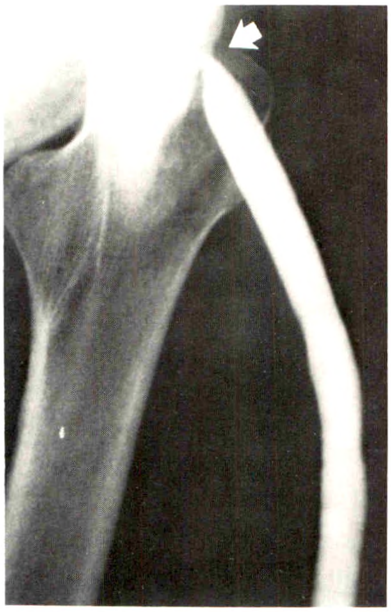

FIG. 3. Stenosis of the bovine heterograft adjacent to the common femoral vein anastomosis.

Discussion

Frequent complications and high failure rate encountered with other types of vascular access for chronic hemodialysis have prompted the search for better methods. Payne, et al.[5] reported 32 patients in whom bovine grafts were used for construction of arteriovenous fistulas. All of their patients had had multiple failures of other types of shunts and fistulas. Haimov and Jacobson[2] reported on 40 grafts in 33 patients who had multiple vascular access procedures performed previously.

In our experience, the modified bovine heterograft has enjoyed improved patient acceptance, high success rate, and relatively low rate of associated complications. The main advantage of the bovine graft has been the effective use in any patient as a means for importantly because of accurate and precise construction of a subcutaneous tunnel. Several patients have had continued bleeding following removal of dialysis needles, but nonoperative treatment with elevation, accurate compression, and additional Protamine administration has served to stop the bleeding in most instances. Continued external bleeding, limb enlargement, distal ischemia, or poor fistula flow would be obvious indications for reoperation.

Mortality. Fourteen patients in this series have died. None of the deaths have been directly attributable to the use of the modified bovine heterograft. Three patients refused dialysis at 3, 5, and 9 weeks after insertion of heterografts and died of complications of renal failure. Two patients could not be resuscitated after cardiac arrest was precipitated by hyperkalemia. One patient with severe uremia developed an acute cardiac tamponade and died. An air embolus was inadvertently introduced during initiation of hemodialysis in another patient, and this caused cardiac standstill and death. Another patient developed upper gastrointestinal hemorrhage and died later of operative complications. An elderly male suffered an acute myocardial infarction during the insertion of the graft and died of cardiac failure 16 days later. Two middle-aged diabetic females died of sepsis following prolonged hospitalization. One died from complications from a perforated colonic diverticulum, and another died from complications associated with the amputation of a gangrenous lower extremity. Two elderly patients with functioning fistulas could not tolerate the hemodynamic changes associated with dialysis and died of multiple system failure. Acute myocardial infarction was the cause of death in another patient 4 months after insertion of the graft.

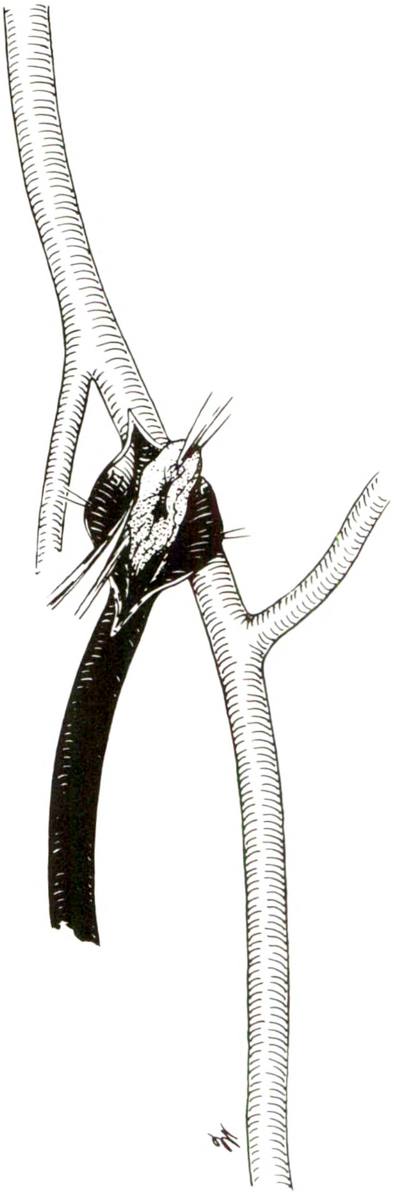

FIG. 4. Method of removal of pseudo-intimal fibrous tissue.

mediate dialysis. We initially preferred to wait several weeks after placement of the graft to allow for wound healing before it was used for hemodialysis. Circumstances arose, however, in which the graft had to be used within several days after surgery, and we now have dialyzed patients several hours after construction of the bovine arteriovenous fistulas. No complications have been seen from this early use of the graft, provided that meticulous hemostasis was obtained at the time of surgery and careful regulation of anticoagulants was performed during dialysis.

The phenomenon of fibrous pseudo-intimal proliferation within the graft may continue to be a significant factor in causing late thrombosis. It has developed in all cases in which grafts have been removed because of infection and in which grafts have been explored for thrombosis or stenosis. The degree to which this fibrous growth produces clinical signs, however, is variable. Further refinement in surgical procedure by lengthening the venotomy may alter flow characteristics and reduce turbulence so that this obstructing lesion is minimized.

Our own observations and the complications reported by Payne[5] and by Haimov and Jacobson,[2] emphasize the extreme importance for precise preoperative surgical judgment in selecting the location for placement of the bovine heterograft. We have had 3 patients with ischemia of the hand but all have improved without resorting to removal or ligation of the fistula. In selecting the graft location, the possibility of precipitating vascular insufficiency should be considered. Important factors related to graft site locations are: the presence or absence of adequate collateral circulation; previous arterial or venous surgery; factors predisposing to progressive atherosclerotic disease, such as diabetes mellitus; type of activity or employment; and the dominance or nondominance of the extremity. Unless previous cannulas, radiocephalic fistulas, saphenous vein or bovine graft arteriovenous fistulas have used available vessels, the fistula should not be located in the dominant extremity. Careful evaluation of the vascular system is an absolute prerequisite to arteriovenous fistula construction.

Our procedure of choice has been and remains the straight forearm fistula. However, we do not agree with Haimov and Jacobson[2] that the loop forearm fistula is "hemodynamically wrong," because our patency rate with this type of fistula has been excellent. It was our procedure of choice with patients having diabetes mellitus because of progressive atherosclerosis so commonly seen in these patients but with three patients developing ischemia of the hand following construction of this type of fistula, we have returned to doing the straight forearm fistula in diabetic patients provided the radial artery is satisfactory for anastomosis.

The bovine heterograft has had a longer and more effective patency rate than when a saphenous vein has been used. It has a distinct advantage over saphenous vein rerouting in that it decreased operative time, there is less surgical trauma, and the heterograft fistula can be easily cannulated soon after placement. The modified bovine heterograft has proved to be an acceptable fistula for hemodialysis.

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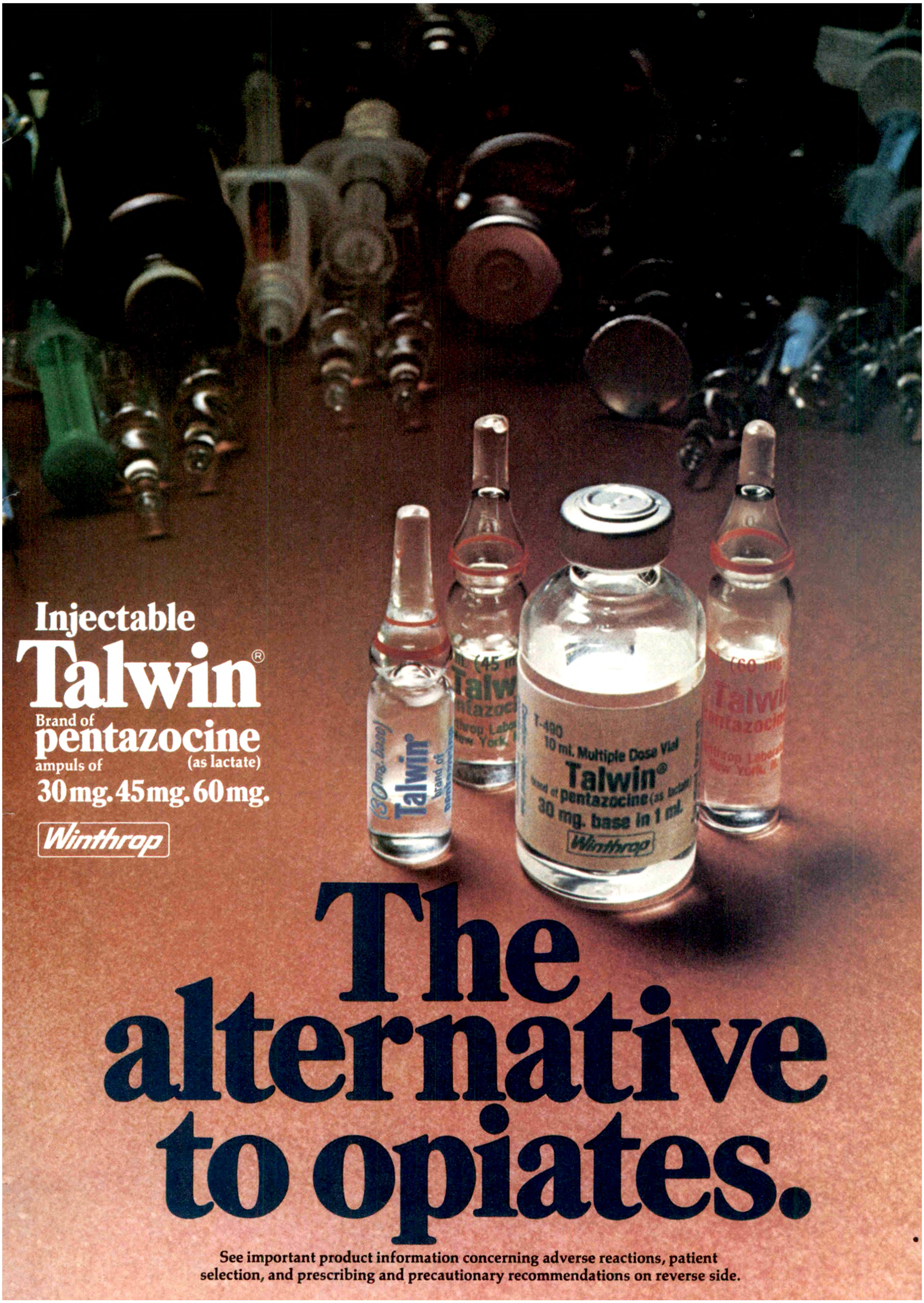

Injectable
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Brand of
pentazocine
ampuls of (as lactate)
30 mg. 45 mg. 60 mg.
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The alternative to opiates.

See important product information concerning adverse reactions, patient selection, and prescribing and precautionary recommendations on reverse side.

•Talwin®
Brand of **pentazocine** (as lactate)
Analgesic for Parenteral Use

Ampuls: 30 mg. (1 ml.), 45 mg. (1½ ml.), and 60 mg. (2 ml.)
Vials: (10 ml.) 30 mg./ml.
30 mg. for I.V., I.M., or S.C. use
45 mg. for I.M. or S.C. use
60 mg. for I.M. or S.C. use

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided. In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain. Just as with all medication, the oral form of Talwin is preferable for chronic administration.*

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. As with all strong analgesics, Talwin should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Tissue Damage at Injection Sites. Severe sclerosis of the skin, subcutaneous tissues, and underlying muscle have occurred at the injection sites of patients who have received multiple doses of pentazocine, as lactate. Constant rotation of injection sites is, therefore, recommended. In addition, animal studies have suggested that Talwin may be tolerated less well subcutaneously than intramuscularly.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Dermatologic Reactions. Soft tissue induration, nodules, and cutaneous depression can occur at injection sites. Ulceration (sloughing) and severe sclerosis of the skin and subcutaneous tissues (and, rarely, underlying muscle) have been reported after multiple doses.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromu cular and psychiatric:* muscle tremor, insomni disorientation, hallucinations; *gastrointestin* taste alteration, diarrhea and cramps; *ophth mic:* blurred vision, nystagmus, diplopia, miosi *hematologic:* depression of white blood cel (especially granulocytes), which is usually r versible, moderate transient eosinophilia; *othe* tachycardia, weakness or faintness, chills, alle gic reactions including angioedema, edema the face, vascular purpura, toxic epiderm necrolysis.

See *Acute CNS Manifestations* and *Drug Depe dence* under **WARNINGS.**

Dosage and Administration: *Adults, Excludi Patients in Labor.* The recommended single pa enteral dose is 30 mg. by intramuscular, subcut neous, or intravenous route. This may repeated every 3 to 4 hours. Doses in excess 30 mg. intravenously or 60 mg. intramuscular or subcutaneously are not recommended. Tot daily dosage should not exceed 360 mg. Wh frequent daily injections are needed over a pr longed period, intramuscular administration preferable to subcutaneous. In addition, consta rotation of injection sites (e.g., the upper out quadrants of the buttocks, mid-lateral aspects the thighs, and the deltoid areas) is reco mended.

Patients in Labor. A single, intramuscular 30 m dose has been most commonly administered. intravenous 20 mg. dose has given adequa pain relief to some patients in labor when co tractions become regular, and this dose may given two or three times at two- to three-ho intervals, as needed.

Children Under 12 Years of Age. Since clinic experience in children under twelve years age is limited, the use of Talwin in this a group is not recommended.

CAUTION. Talwin should not be mixed in t same syringe with soluble barbiturates becau precipitation will occur.

Overdosage: *Manifestations.* Clinical experien with Talwin overdosage has been insufficient define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopre sors, and other supportive measures should employed as indicated. Assisted or controll ventilation should also be considered. Althou nalorphine and levallorphan are *not* effective an dotes for respiratory depression due to overdo age or unusual sensitivity to Talwin, parenter naloxone (Narcan®, available through Endo La oratories) is a specific and effective antagoni

Talwin is not subject to narcotic controls.

How Supplied: *Uni-Amp®—Individual unit do ampuls of 1 ml. (30 mg.) and 2 ml. (60 mg.)* boxes of 25.

Ampuls of 1 ml. (30 mg.) in (nested) boxes of 2

Ampuls of 1½ ml. (45 mg.) in boxes of 10 and 10

Ampuls of 2 ml. (60 mg.) in (nested) boxes of 2

Each 1 ml. contains Talwin (brand of pentaz cine) as lactate equivalent to 30 mg. base a 2.8 mg. sodium chloride, in water for injectio

Multiple dose vials of 10 ml., each 1 ml. co taining Talwin (brand of pentazocine) as lacta equivalent to 30 mg. base, 2 mg. acetone sodiu bisulfite, 1.5 mg. sodium chloride, and 1 m methylparaben as preservative, in water for i jection. Boxes of 1.

The pH of Talwin solutions is adjusted betwe 4 and 5 with lactic acid and sodium hydroxid The air in the ampuls and vials has been di placed by nitrogen gas.

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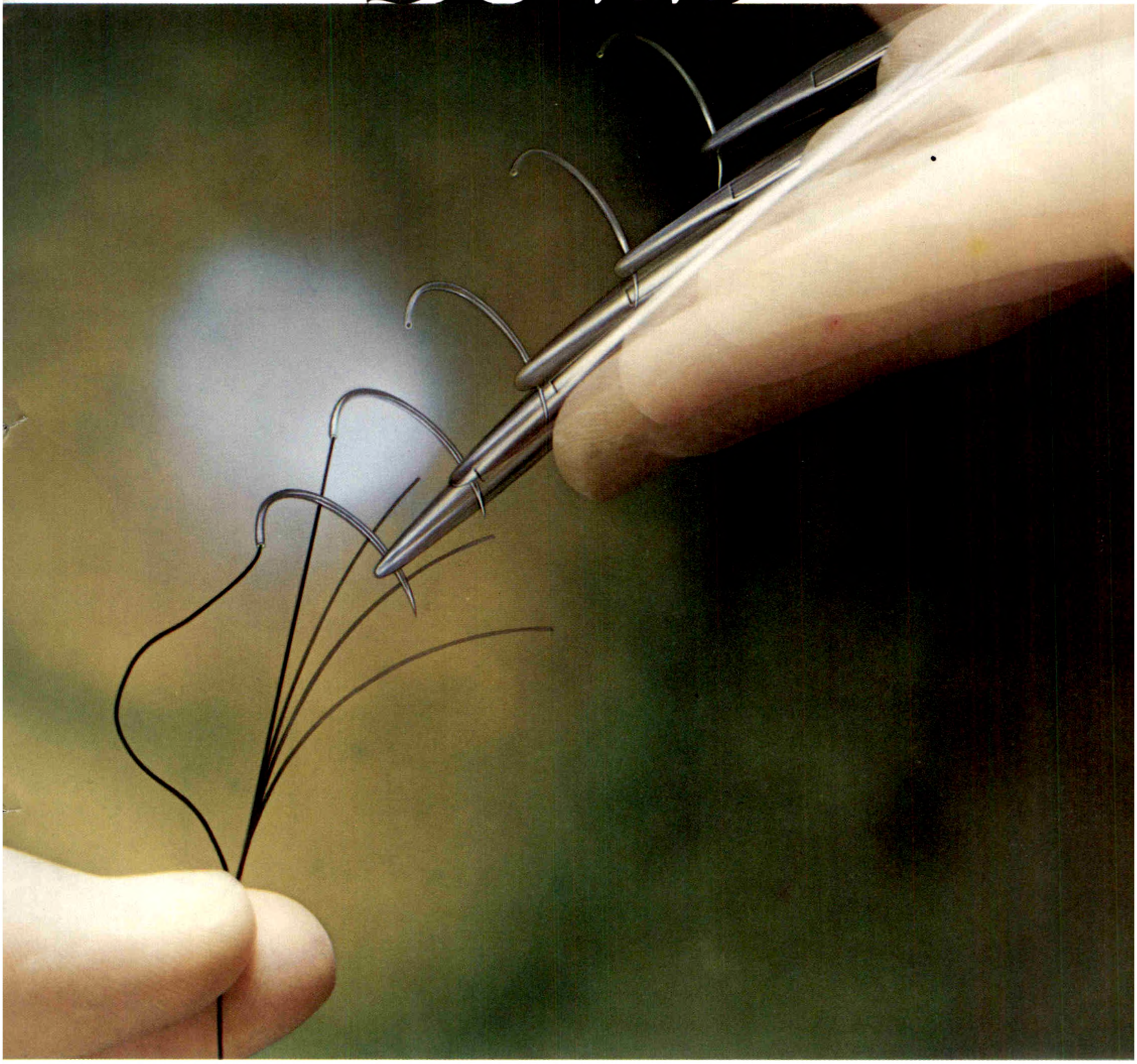

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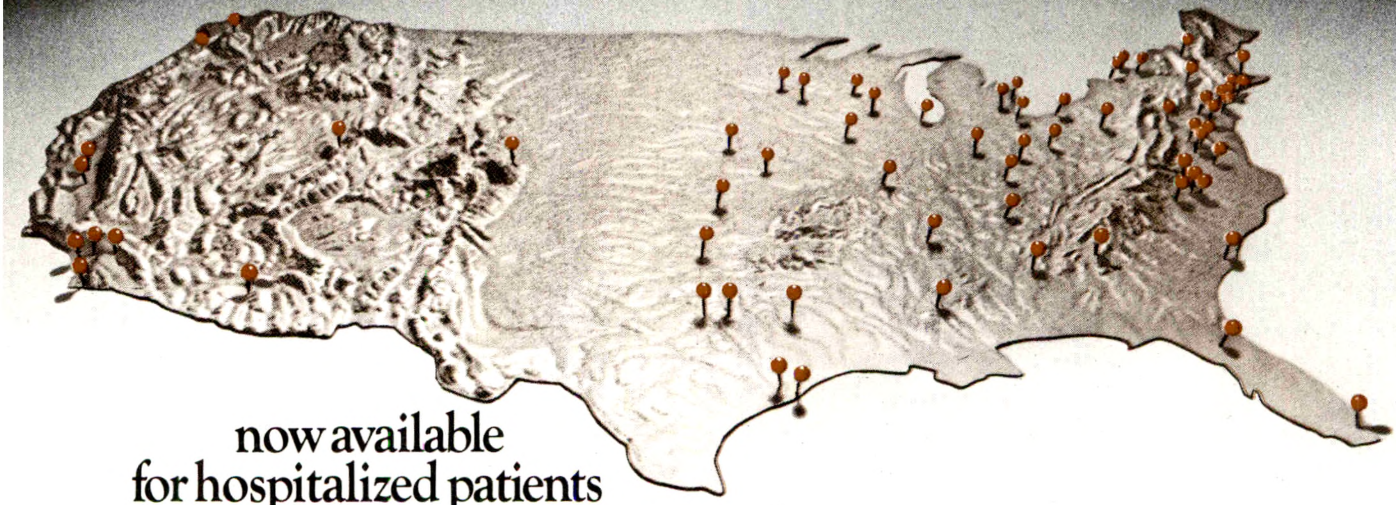

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WARNINGS

Patients treated with Nebcin® (tobramycin sulfate, Lilly) should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.

Both vestibular and auditory ototoxicity can occur. Eighth-nerve impairment may develop if patients have preexisting renal damage and if Nebcin is administered for longer periods or in higher doses than those recommended.

Tobramycin is potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by cylindruria, oliguria, proteinuria, or evidence of nitrogen retention (increasing BUN, NPN, or creatinine). Evidence of impairment in renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.

Nebcin should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.

In the case of overdosage or toxic reactions, peritoneal dialysis or hemodialysis will help remove tobramycin from the blood.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 12 mcg./ml. should be avoided. Urine should be examined for increased excretion of protein, cells, and casts.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, and colistin, should be avoided.

Nebcin should not be given concurrently with potent diuretics. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Nebcin® ◆ I.M./I.V.

tobramycin sulfate

Lilly

500779

for serious infections including

septicemia

Bacterial cultures should be obtained prior to and during treatment. In patients in whom gram-negative septicemia or neonatal sepsis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with Nebcin may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with Nebcin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the WARNINGS box in the prescribing information.

lower-respiratory-tract infections

Nebcin is indicated in bronchopneumonia, pneumonia, empyema, and bronchitis. Most patients treated in clinical trials had one or more of the following underlying respiratory tract conditions: asthma, cor pulmonale, cystic fibrosis, emphysema, bronchiectasis, lung cancer, empyema, and respiratory tract anomaly.

urinary tract infections

Nebcin is indicated in the treatment of serious complicated and recurrent urinary tract infections. Aminoglycosides, including Nebcin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity.

caused by susceptible strains of

Pseudomonas aeruginosa
Klebsiella-Enterobacter-Serratia
  group
Escherichia coli
Proteus sp. (indole-positive and
  indole-negative)
Providencia sp.
Citrobacter sp.
Group D streptococci
Staphylococci,* including
  Staphylococcus aureus
  (coagulase-positive and
  coagulase-negative)

*Nebcin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Please see following page for summary of prescribing information.

Nebcin® ♦ I.M./I.V.
tobramycin sulfate

Prescribing Information

WARNINGS

Patients treated with Nebcin should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.

Both vestibular and auditory ototoxicity can occur. Eighth-nerve impairment may develop if patients have preexisting renal damage and if Nebcin is administered for longer periods or in higher doses than those recommended.

Tobramycin is potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by cylindruria, oliguria, proteinuria, or evidence of nitrogen retention (increasing BUN, NPN, or creatinine). Evidence of impairment in renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.

Nebcin should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.

In the case of overdosage or toxic reactions, peritoneal dialysis or hemodialysis will help remove tobramycin from the blood.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 12 mcg./ml. should be avoided. Urine should be examined for increased excretion of protein, cells, and casts.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, and colistin, should be avoided.

Nebcin should not be given concurrently with potent diuretics. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Description: Tobramycin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from the actinomycete *Streptomyces tenebrarius*. Nebcin Injection is a clear and colorless sterile aqueous solution for parenteral administration. It is stable and requires no refrigeration.

Indications and Usage: Nebcin is indicated for the treatment of serious infections caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa, Escherichia coli, Proteus* sp. (indole-positive and indole-negative), *Providencia, Klebsiella-Enterobacter-Serratia* group, *Citrobacter* sp., group D streptococci, and staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).

Nebcin is indicated in the treatment of septicemia; central-nervous-system infections, including meningitis; neonatal sepsis; serious lower respiratory infections; gastrointestinal infections, including peritonitis; and serious skin, bone, and soft-tissue infections, including burns, caused by the susceptible organisms listed above. Clinical studies have shown Nebcin also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including Nebcin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity. Nebcin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Bacterial cultures should be obtained prior to and during treatment to isolate and identify etiologic organisms and to test their susceptibility to tobramycin. If susceptibility tests show that the causative organisms are resistant to tobramycin, other appropriate therapy should be instituted. In patients in whom gram-negative septicemia, neonatal sepsis, or meningitis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with Nebcin may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with Nebcin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the WARNINGS box above.

Contraindication: A history of hypersensitivity to tobramycin is a contraindication to its use.

Warnings: See WARNINGS box above.

Precautions: Specimens should be collected during therapy for examination, as recommended in the WARNINGS box.

Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of tobramycin (40 mg./Kg.). The possibility that these phenomena may occur in man should be considered if tobramycin is administered to patients who are also receiving neuromuscular blocking agents, such as succinylcholine or tubocurarine.

Cross-allergenicity among aminoglycosides has been demonstrated.

If overgrowth of nonsusceptible organisms occurs, appropriate therapy should be initiated.

Adverse Reactions: *Nephrotoxicity*—Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, cylindruria, and increased proteinuria, have been reported, especially in patients with a history of renal impairment who are treated for longer periods or with higher doses than those recommended.

Neurotoxicity—Adverse effects on both the vestibular and auditory branches of the eighth nerve have been noted, especially in patients receiving high doses or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss.

NOTE: The risk of toxic reactions is low in patients with normal renal function who do not receive Nebcin in higher doses or for longer periods of time than those recommended.

Other reported adverse reactions possibly related to Nebcin include increased serum transaminase (SGOT, SGPT) and increased serum bilirubin; anemia, granulocytopenia, and thrombocytopenia; and fever, rash, itching, urticaria, nausea, vomiting, headache, and lethargy.

Suggested Dosage Guides—I.M./I.V.:

Usual dosage for adults, children, and older infants (normal renal function)—

3 mg./Kg./day administered in three equal doses every eight hours. In life-threatening situations, the dosage may be increased up to 5 mg./Kg./day administered in three or four equal doses. This dosage should be reduced to 3 mg./Kg./day as soon as clinically indicated. (Refer to Table 1 for dosage schedule.)

Dosage for neonates up to one week of age (normal renal function)—

Up to 4 mg./Kg./day may be given in two equal doses every twelve hours. The usual duration of treatment is seven to ten days.

Dosage guidelines for adult or pediatric patients with reduced renal function—

After a loading dose of 1 mg./Kg., subsequent dosage must be adjusted either with reduced doses at eight-hour intervals or with normal doses at prolonged intervals. To determine the reduced dose at eight-hour intervals, see the convenient nomogram in the package literature.[*] To calculate normal dosage at prolonged intervals (if the creatinine clearance rate is not available and the patient's condition is stable), the following formula may be used:

1 mg./Kg. q. (6 × serum creatinine) h.

Neither regimen should be used when dialysis is being performed.

I.V. Administration—The usual volume of diluent for adults is 50 to 100 ml. For children, the volume of diluent should be proportionately less than for adults. The diluted solution usually should be infused over a period of twenty to sixty minutes.

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[*] An alternate rough guide for determining reduced dosage at eight-hour intervals (for patients whose steady-state serum creatinine values are known) is to divide the normally recommended dose by the patient's serum creatinine.

Table 1. Dosage Schedule Guide for Adults with Normal Renal Function (Dosage at Eight-Hour Intervals)

For Patient Weighing		Usual Dose for Serious Infections 1 mg./Kg. q. 8 h. (Total, 3 mg./Kg./day)		Maximum Dose for Life-Threatening Infections **(Reduce as soon as possible)** 1.66 mg./Kg. q. 8 h. (Total, 5 mg./Kg./day)	
Kg.	Lb.	**mg./dose q. 8 h.**	**ml./dose[†]**	**mg./dose q. 8 h.**	**ml./dose[†]**
120	264	120 mg.	3 ml.	200 mg.	5 ml.
115	253	115 mg.	2.9 ml.	191 mg.	4.75 ml.
110	242	110 mg.	2.75 ml.	183 mg.	4.5 ml.
105	231	105 mg.	2.6 ml.	175 mg.	4.4 ml.
100	220	100 mg.	2.5 ml.	166 mg.	4.2 ml.
95	209	95 mg.	2.4 ml.	158 mg.	4 ml.
90	198	90 mg.	2.25 ml.	150 mg.	3.75 ml.
85	187	85 mg.	2.1 ml.	141 mg.	3.5 ml.
80	176	80 mg.	2 ml.	133 mg.	3.3 ml.
75	165	75 mg.	1.9 ml.	125 mg.	3.1 ml.
70	154	70 mg.	1.75 ml.	116 mg.	2.9 ml.
65	143	65 mg.	1.6 ml.	108 mg.	2.7 ml.
60	132	60 mg.	1.5 ml.	100 mg.	2.5 ml.
55	121	55 mg.	1.4 ml.	91 mg.	2.25 ml.
50	110	50 mg.	1.25 ml.	83 mg.	2.1 ml.
45	99	45 mg.	1.1 ml.	75 mg.	1.9 ml.
40	88	40 mg.	1 ml.	66 mg.	1.6 ml.

[†] Applicable to all product forms except Nebcin, Pediatric, Injection (see How Supplied).

How Supplied: Ampoules Nebcin® (tobramycin sulfate, Lilly) Injection, 80 mg. (equivalent to tobramycin) per 2 ml., 2 ml., rubber-stoppered.

Ampoules Nebcin, Pediatric, Injection, 20 mg. (equivalent to tobramycin) per 2 ml., 2 ml., rubber-stoppered.

Hyporets® (disposable syringes, Lilly) Nebcin Injection, 60 mg. (equivalent to tobramycin) per 1.5 ml., 1.5 ml., and 80 mg. (equivalent to tobramycin) per 2 ml., 2 ml., in packages of 24.

Each ml. also contains 5 mg. phenol as a preservative, 3.2 mg. sodium bisulfite, 0.1 mg. disodium edetate, and water for injection, q.s. Sulfuric acid and/or sodium hydroxide may have been added to adjust the pH. [063075]

Lilly

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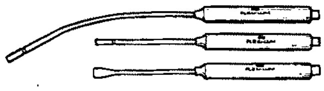

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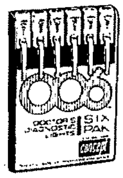

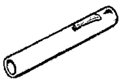

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Recent advances in pathophysiology, diagnosis and treatment of surgical disease for the general surgeon. Topics include theory and practice of abdominal, vascular, thoracic, trauma and tumor surgery, and basic principles of pre and postoperative care.

For details, write or phone: Office of Associate Dean, Dept. N, NYU Post-Graduate Medical School, 550 First Avenue, NYC, NY 10016 (212) 679-3200, ext. 4033.

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: Tigan is indicated for the control of nausea and vomiting.

CONTRAINDICATIONS: The injectable form of Tigan in children, the suppositories in premature or newborn infants, and use in patients with known hypersensitivity to trimethobenzamide are contraindicated. Since the suppositories contain benzocaine they should not be used in patients known to be sensitive to this or similar local anesthetics.

WARNINGS: Tigan may produce drowsiness. Patients should not operate motor vehicles or other dangerous machinery until their individual responses have been determined. Reye's Syndrome has been associated with the use of Tigan and other drugs, including antiemetics, although their contribution, if any, to the cause and course of the disease hasn't been established. This syndrome is characterized by an abrupt onset shortly following a nonspecific febrile illness, with persistent severe vomiting, lethargy, irrational behavior, progressive encephalopathy leading to coma, convulsions and death.

Usage in Pregnancy: Trimethobenzamide hydrochloride was studied in reproduction experiments in rats and rabbits and no teratogenicity was suggested. The only effects observed were an increased percentage of embryonic resorptions or stillborn pups in rats administered 20 mg and 100 mg/kg and increased resorptions in rabbits receiving 100 mg/kg. In each study these adverse effects were attributed to one or two dams. The relevance to humans is not known. Since there is no adequate experience in pregnant or lactating women who have received this drug, safety in pregnancy or in nursing mothers has not been established.

PRECAUTIONS: During the course of acute febrile illness, encephalitides, gastroenteritis, dehydration and electrolyte imbalance, especially in children and the elderly or debilitated, CNS reactions such as opisthotonos, convulsions, coma and extrapyramidal symptoms have been reported with and without use of Tigan or other antiemetic agents. In such disorders caution should be exercised in administering Tigan, particularly to patients who have recently received other CNS-acting agents (phenothiazines, barbiturates, belladonna derivatives). It is recommended that severe emesis should not be treated with an antiemetic drug alone; where possible the cause of vomiting should be established. Primary emphasis should be directed toward the restoration of body fluids and electrolyte balance, the relief of fever and relief of the causative disease process. Overhydration should be avoided since it may result in cerebral edema.

The antiemetic effects of Tigan may render diagnosis more difficult in such conditions as appendicitis and obscure signs of toxicity due to overdosage of other drugs.

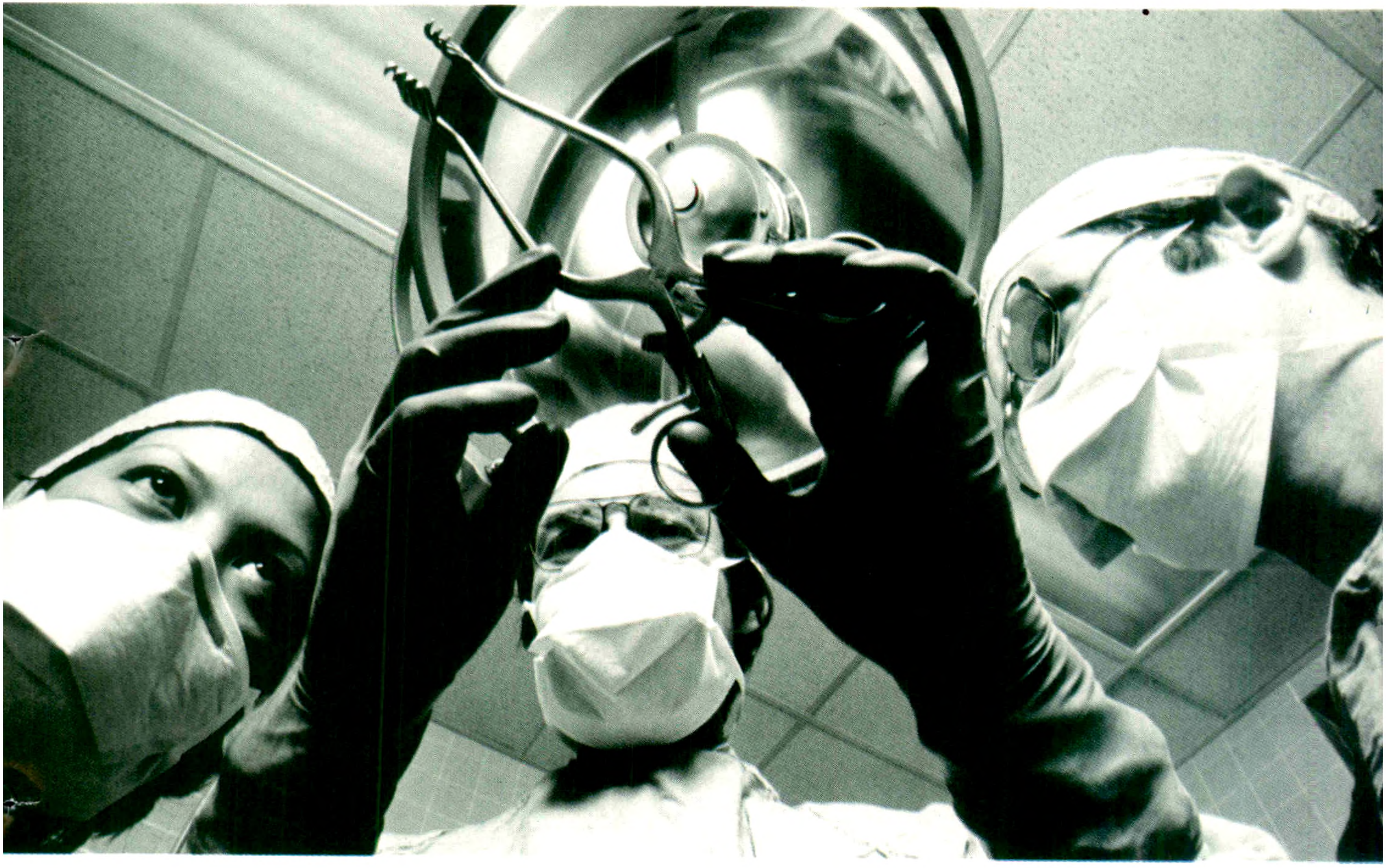
ADVERSE REACTIONS: There have been reports of hypersensitivity reactions and Parkinson-like symptoms. There have been instances of hypotension reported following parenteral administration to surgical patients. There have been reports of blood dyscrasias, blurring of vision, coma, convulsions, depression of mood, diarrhea, disorientation, dizziness, drowsiness, headache, jaundice, muscle cramps and opisthotonos. If these occur, the administration of the drug should be discontinued. Allergic-type skin reactions have been observed; therefore, the drug should be discontinued at the first sign of sensitization. While these symptoms will usually disappear spontaneously, symptomatic treatment may be indicated in some cases.

HOW SUPPLIED: Ampuls, 2 ml, boxes of 10. Multiple Dose Vials, 20 ml. Thera-Ject™ (Disposable Syringes), 2 ml, boxes of 10.

Many things have changed in the operating room in 15 years...

but the Tigan effect hasn't.

(trimethobenzamide HCl)



When Tigan was introduced in 1959, nausea or vomiting was a frequent postoperative occurrence. Advances in surgical technique and anesthetic agents have reduced these incidences. However, when you need control of emesis and need it quickly, Tigan provides the necessary effectiveness with a relative lack of side effects.

Tigan has been used successfully with many different anesthetics and in all types of surgery without potentiating the anesthesia, delaying the awakening or altering the patient's vital signs (although a few instances of hypotension have been reported).

Tigan Injectable is intended for intramuscular administration only: the recommended adult dose—2 ml. (200 mg.) t.i.d. or q.i.d. (It is contraindicated in children)

For prompt control of nausea and vomiting

Tigan® Injectable.

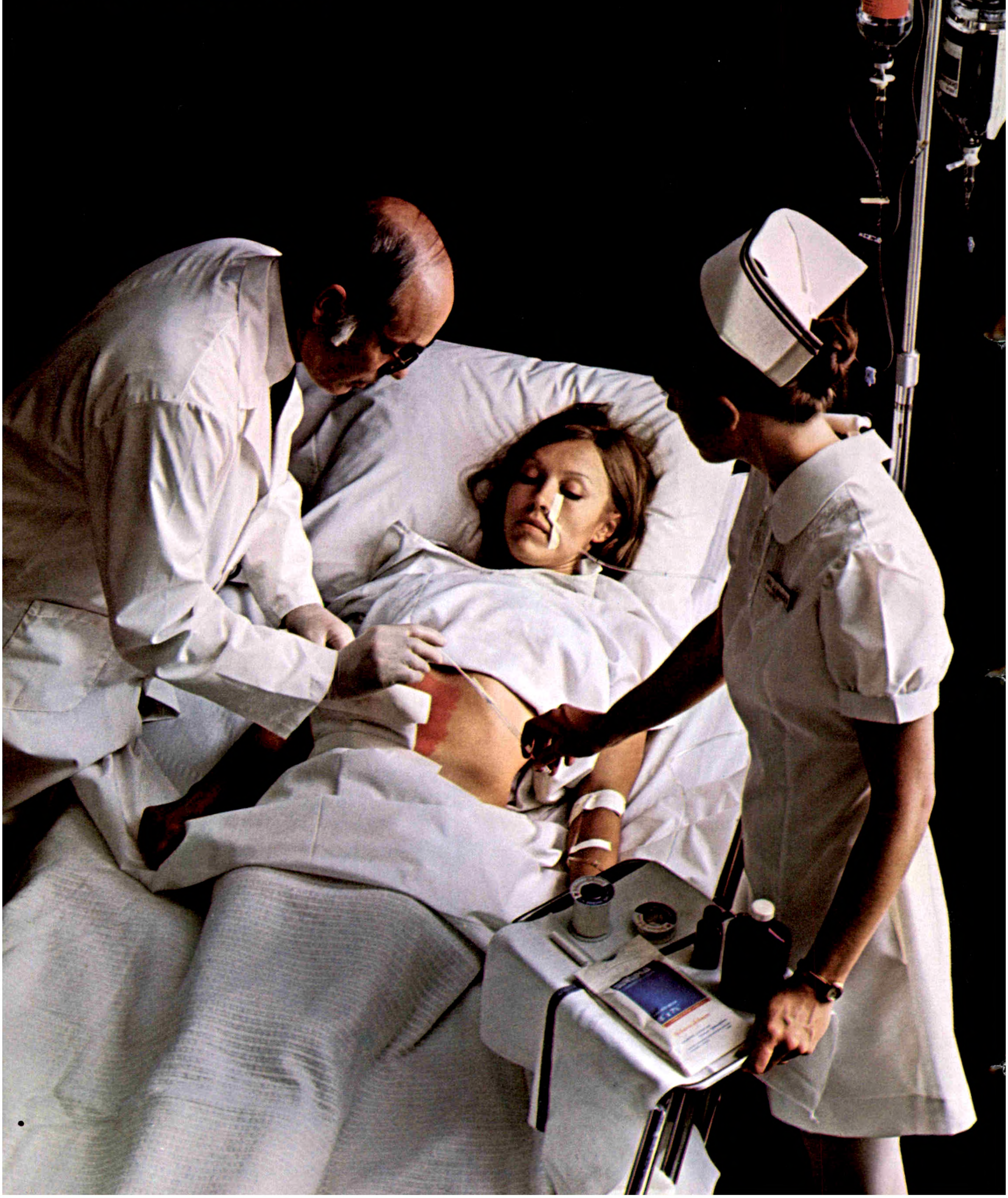
(trimethobenzamide HCl)

Please see adjoining page for Brief Summary.

Beecham
laboratories, Bristol, Tennessee 37620

In serious post-surgical infections*...

*due to indicated susceptible organisms



Until the lab tests come back, start with 'ANCEF'

Serious post-surgical infections usually require immediate treatment. In these cases prudent medical judgment and the use of 'Ancef', when appropriate, can save valuable time while waiting for lab results. 'Ancef' offers:

- **Broad coverage of the major areas of post-surgical infection**

  Skin and Soft-Tissue Infections:
  Staphylococcus aureus (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

  Respiratory Tract Infections:
  Streptococcus pneumoniae (formerly *D. pneumoniae*), *Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

  Urinary Tract Infections:
  E. coli, Proteus mirabilis, Klebsiella species and some strains of enterobacter and enterococci.

- **High and prolonged serum levels**
  Single 1 gram IV injections in healthy adult volunteers produced average peak serum levels of 190.0 mcg/ml. At four hours, levels of 16.5 mcg/ml were still present.

- **Convenient IV or IM administration at same dosage schedule**

When lab tests return, if the indicated organism is sensitive to 'Ancef'—and chances are it will be—therapy is already under way. If it isn't sensitive, then 'Ancef' should be discontinued and an appropriate antibiotic should be selected.

Adverse Reactions
Reported adverse reactions include pain on injection, rash, G.I. symptoms, pruritus and phlebitis. For a complete list of reported adverse reactions, please see next page.

Warning: In penicillin-sensitive patients, cephalosporins should be used with caution because of evidence of partial cross-allergenicity of the penicillins and cephalosporins.

Please see next page for a brief summary of prescribing information.

SK&F Smith Kline & French Laboratories
Division of SmithKline Corporation, Philadelphia, Pa.

ANCEF® IV/IM

brand of sterile

CEFAZOLIN SODIUM

(LYOPHILIZED)

Injection: 250 mg, 500 mg, and 1 gram vials

ANCEF® IV IM

brand of sterile

CEFAZOLIN SODIUM

(LYOPHILIZED)

Injection: 250 mg, 500 mg, and 1 gram vials

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

DESCRIPTION

Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro:*

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant).

Streptococcus pneumoniae (formerly *D. pneumoniae)*
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole positive Proteus *(P. vulgaris, P. morgani, P. rettgeri)* are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Streptococcus pneumoniae* (formerly *D. pneumoniae), Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx, however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus.*

Septicemia due to *Streptococcus pneumoniae* (formerly *D. pneumoniae), Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE CEFAZOLIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to 'Ancef'.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported.

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for pneumococcal pneumonia is 500 mg. every 12 hours. In acute, uncomplicated urinary tract infections, usual dosage is 1 gram every 12 hours. In mild infections caused by susceptible Gram positive cocci, usual dosage is 250 to 500 mg. every 8 hours. In moderate to severe infections, usual dosage is 500 mg. to 1 gram every 6 to 8 hours. 'Ancef' has been administered in dosages of 6 grams per day in serious infections such as endocarditis.

'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 ml./min. or greater or a serum creatinine of 1.5 mg. % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 ml./min. or serum creatinine of 1.6 to 3.0 mg. % can also be given full doses, but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11 to 34 ml./min. or serum creatinine of 3.1 to 4.5 mg. % should be given 1/2 the usual dose every 12 hours. Patients with creatinine clearance rates of 10 ml./min. or less or serum creatinine of 4.6 mg. % or greater should be given 1/2 the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

HOW SUPPLIED

Ancef (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg. or 1 gram of cefazolin; in Overfill ("piggyback") Vials for intravenous admixture equivalent to 1 gram of cefazolin; and in Pharmacy Bulk Vials equivalent to 5 grams or 10 grams of cefazolin.

Smith Kline & French Laboratories
Division of SmithKline Corporation, Philadelphia, Pa.
SK&F

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SURGILON. The braided nylon suture you can use like silk.

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that may heighten

Postop Pain

Surgical aftercare can be smoother with Vistaril I.M. (hydroxyzine HCl). It helps allay the excessive anxiety that can heighten the patient's perception of [redacted] and helps assure calm and cooperative patients. Vistaril I.M. also helps minimize secondary postoperative complaints, and often relieves postoperative confusion.

Vistaril I.M. may enhance the effect of injectable analgesics, such as meperidine, morphine sulfate and pentazocine. It has no significant depressant effects on respiratory or circulatory function and often reduces postoperative emesis.

It is [redacted]cally compatible with most commonly used analgesics, and can be mixed with them in the same syringe.

Alone, or as an adjunct for use in the management of postoperative pain, the maximum recommended dosage of Vistaril I.M. is 100 mg. While the analgesic dosage needed will usually be reduced, the actual dosage of Vistaril I.M. should be titrated against the individual patient's clinical response.

Vistaril® I.M.
(hydroxyzine HCl)

100 mg./2 ml., 50 mg./ml. and 25 mg./ml.
Vials and Isojects®

Pfizer LABORATORIES DIVISION
PFIZER INC

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.

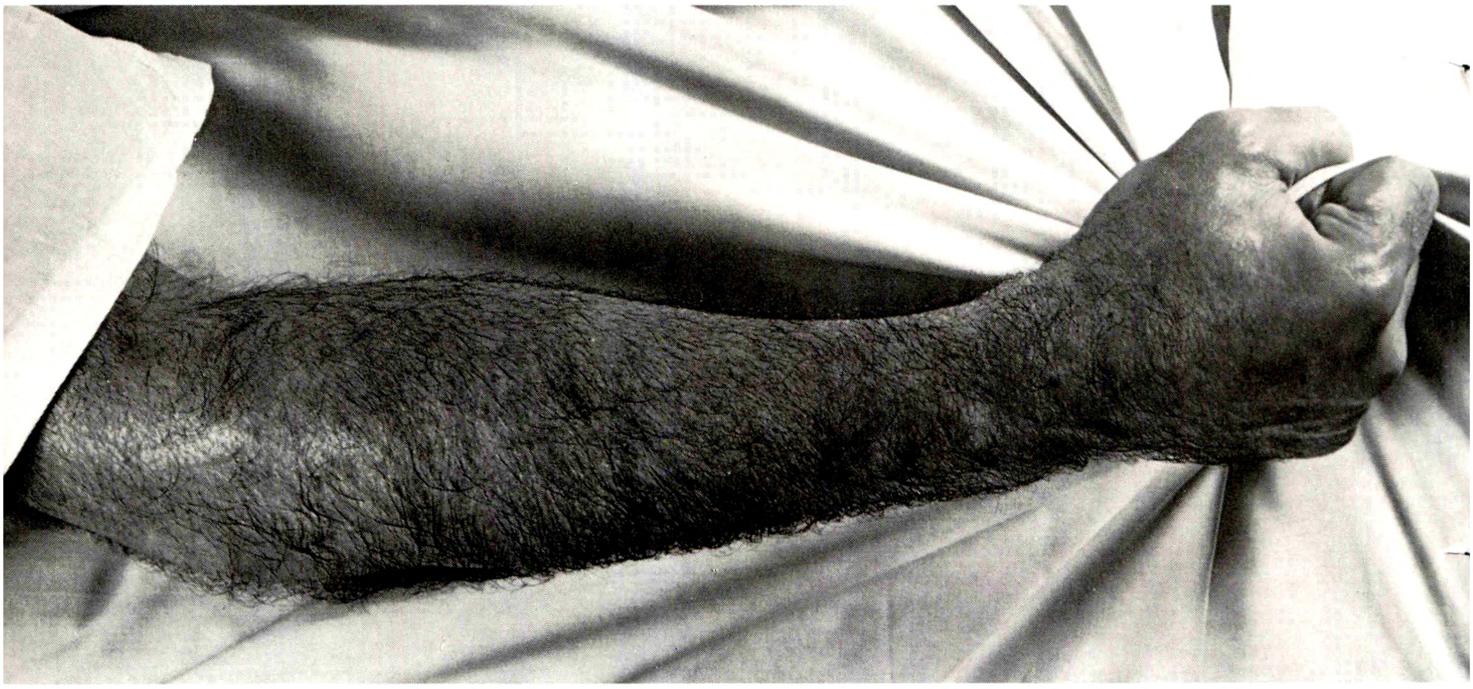
Vistaril® I.M.
(hydroxyzine HCl)

100 mg./2 ml., 50 mg./ml. and 25 mg./ml.
Vials and Isojects®

helps relieve the anxiety associated with postoperative pain

may enhance narcotic effect

offers proved antiemetic action



Brief Summary
VISTARIL® (hydroxyzine hydrochloride) Intramuscular Solution
For Intramuscular Use Only

Contraindications: Hypersensitivity to hydroxyzine. The solution for intramuscular use *must not* be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: *Hydroxyzine may potentiate the action of central nervous system depressants such as narcotics and barbiturates.* In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used.

Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and only with caution to avoid radial nerve injury. Injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid intravascular injection.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg./ml.—10 ml. vial; 50 mg./ml.—2 ml. and 10 ml. vial; Isoject®, 25 mg./ml. and 50 mg./ml., 1 ml. fill; 100 mg./2 ml., 2 ml. fill.

Military Depot: NSN 6505-00-052-1367 (50 mg./ml., 10 ml. vial)
VA Depot: NSN 6505-00-052-1367B (50 mg./ml., 10 ml. vial)

More detailed professional information available on request.

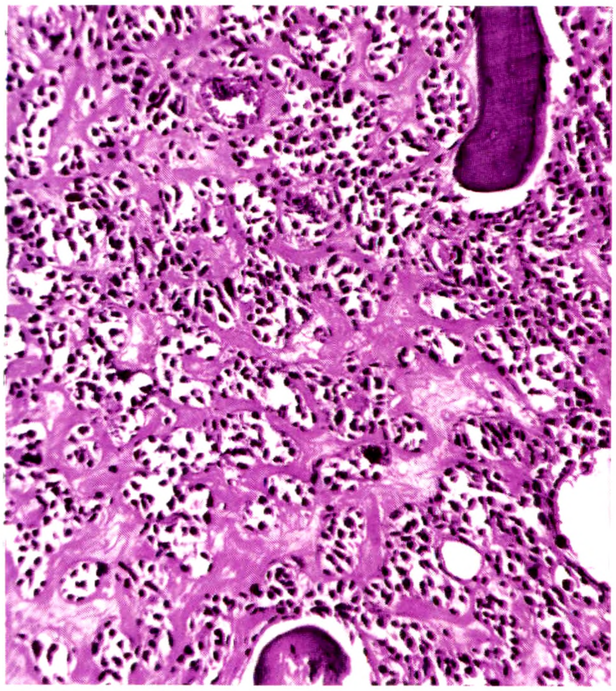
Pfizer LABORATORIES DIVISION
PFIZER INC.

Adriamycin™
(doxorubicin HCl) for injection

FOR INTRAVENOUS USE ONLY

10 mg and 50 mg vials

active against a number of solid tumors as well as certain hematologic malignancies



OSTEOGENIC SARCOMA
Nests of sarcoma cells surrounded by osteoid. Parts of two normal trabeculae remain. (Hematoxylin and eosin stain.)

For complete prescribing information, please see the following page.

In addition to osteogenic sarcoma, neoplastic conditions that have responded to Adriamycin include: acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, soft tissue sarcoma, neuroblastoma, ovarian carcinoma, transitional cell bladder tumor, bronchogenic lung carcinoma, thyroid carcinoma, lymphoma of both Hodgkin and non-Hodgkin type and breast carcinoma.

Like other cytotoxic agents, Adriamycin should be used only under the direction of specialists qualified in the administration of such drugs.

Severe local tissue necrosis will occur if there is extravasation during administration.

Serious irreversible myocardial toxicity has occurred, especially in patients who have received more than the recommended cumulative dosage.

The incidence of bone marrow depression is high. Hematopoietic toxicity may limit dosage.

In patients with impaired hepatic function, dosage should be reduced.

Complete alopecia usually accompanies treatment. Stomatitis and esophagitis are common.

For information on the use of Adriamycin, call collect (302) 575-7830.

Or, fill out and mail the coupon below.

Adria Laboratories Inc.
Dept. AS
1105 Market Street
Wilmington, Delaware 19899

Dr. ____________________

Address ____________________

City ____________________ State ________ Zip ________

Specialty ____________________

ADRIAMYCIN™ (doxorubicin hydrochloride) for injection
FOR INTRAVENOUS USE ONLY

> **WARNINGS**
>
> 1. Severe local tissue necrosis will occur if there is extravasation during administration. Adriamycin must not be given by the intramuscular or subcutaneous route.
> 2. Serious irreversible myocardial toxicity with delayed congestive failure often unresponsive to any cardiac supportive therapy may be encountered as total dosage approaches 550 mg/m^2. This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy.
> 3. Dosage should be reduced in patients with impaired hepatic function.
> 4. Severe myelosuppression may occur.
> 5. Adriamycin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

DESCRIPTION

Doxorubicin is a cytotoxic antibiotic isolated from cultures of *Streptomyces peucetius var. caesius*. It is supplied in the hydrochloride form as a freeze-dried powder containing lactose. Doxorubicin hydrochloride is readily soluble in water or physiological saline.

CLINICAL PHARMACOLOGY

Though not completely elucidated, the mechanism of action of doxorubicin is related to its ability to bind to DNA and inhibit nucleic acid synthesis. Cell culture studies have demonstrated rapid cell penetration and perinucleolar chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, mutagenesis and chromosomal aberrations. Animal studies have shown activity in a spectrum of experimental tumors, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including cardiac toxicity in rabbits, myelosuppression in all species and atrophy to testes in rats and dogs. Teratology studies, though not showing a definite increase in specific or nonspecific malformations, indicate a moderate interference with the viability of embryos and fetuses.

Pharmacokinetic studies show the intravenous administration of normal or radiolabeled Adriamycin (doxorubicin hydrochloride) for injection is followed by rapid plasma clearance and significant tissue binding. Urinary excretion, as determined by fluorimetric methods, accounts for approximately 4-5% of the administered dose in five days. Biliary excretion represents the major excretion route, 40-50% of the administered dose being recovered in the bile or the feces in seven days. Impairment of liver function results in slower excretion, and, consequently, increased retention and accumulation in plasma and tissues. Adriamycin does not cross the blood-brain barrier.

INDICATIONS

Adriamycin has been used successfully to produce regression in neoplastic conditions such as: acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, bronchogenic (lung) carcinoma, thyroid carcinoma and lymphomas of both Hodgkin and non-Hodgkin types. A number of other solid tumors have also shown some responsiveness but in numbers too limited to justify specific recommendation. Studies to date have shown malignant melanoma, kidney carcinoma, large bowel carcinoma, brain tumors and metastases to the central nervous system not to be significantly responsive to Adriamycin therapy.

CONTRAINDICATIONS

Adriamycin therapy should not be started in patients who have marked myelosuppression induced by previous treatment with other antiblastic agents or by radiotherapy. Conclusive data are not available on pre-existing heart disease as a co-factor of increased risk of Adriamycin-induced cardiac toxicity. Preliminary data suggest that in such cases cardiac toxicity may occur at doses lower than the recommended cumulative limit. It is therefore not recommended to start Adriamycin in such cases. Adriamycin treatment is contraindicated in patients who received previous treatment with complete cumulative doses of Adriamycin and daunorubicin.

WARNINGS

Special attention must be given to the cardiac toxicity exhibited by Adriamycin. Although uncommon, acute left ventricular failure has occurred, particularly in patients who have received total dosage of the drug exceeding the currently recommended limit of 550 mg/m^2 of body surface. This limit appears to be lower (400 mg/m^2) in children who received radiotherapy to the mediastinal area. The total dose of Adriamycin administered to the individual patient should also take into account any previous or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide or related compounds such as daunorubicin. It should be noted that the cardiac failure may also occur several weeks after administration of the drug and is often not favorably affected by presently known medical or physical therapy for cardiac support. Early clinical diagnosis of drug-induced heart failure appears to be essential for successful treatment with digitalis, diuretics, low salt diet and bed rest. Severe cardiac toxicity may occur precipitously without antecedent EKG changes. Baseline EKG and periodic follow-up EKG during, and immediately after, active drug therapy is an advisable precaution. Transient EKG changes, such as T-wave flattening, S-T depression, and arrhythmias are presently not considered indications for suspension of Adriamycin therapy. A reduction in the voltage of the QRS wave is presently considered more specifically predictive for cardiac toxicity. If this occurs, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

There is a high incidence of bone marrow depression, primarily of leukocytes, requiring careful hematological monitoring. With the recommended dosage schedule, leukopenia is usually transient, reaching its nadir at 10-14 days after treatment with recovery usually occurring by the 21st day. White blood cell counts as low as 1000/mm^3 are to be expected during treatment with appropriate doses of Adriamycin. Red blood cell and platelet levels should also be monitored since they may also be depressed. Hematologic toxicity may require dose reduction or suspension or delay of Adriamycin therapy. Persistent severe myelosuppression may result in superinfection or hemorrhage.

Toxicity to recommended doses of Adriamycin is enhanced by hepatic impairment, therefore, prior to the individual dosing, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase, bilirubin, and BSP (see DOSAGE AND ADMINISTRATION).

On intravenous administration of Adriamycin, a stinging or burning sensation signifies a small degree of extravasation and even if blood return from aspiration of the infusion needle is good, the injection or infusion should be immediately terminated and restarted in another vein.

PRECAUTIONS

Initial treatment with Adriamycin requires close observation of the patient and extensive laboratory monitoring. It is recommended, therefore, that patients be hospitalized at least during the first phase of the treatment.

There is no adequate information on whether this drug may adversely affect fertility in human males or females, or have a teratogenic potential or other adverse effects on the fetus. Experimental data, however, suggest that Adriamycin may reduce the viability of the fetuses, therefore the benefits to the pregnant patient should be weighed against the potential toxicity to fetus and embryo. Adriamycin and related compounds have also been shown to have mutagenic and carcinogenic properties when tested in experimental models.

Adriamycin imparts a red coloration to the urine for 1-2 days after administration and patients should be advised to expect this during active therapy.

Adriamycin is not an antimicrobial agent.

ADVERSE REACTIONS

Dose-limiting toxicities of therapy are myelosuppression and cardiotoxicity (see WARNINGS). Other reactions reported are:

Cutaneous—Reversible complete alopecia occurs in most cases. Hyperpigmentation of nailbeds and dermal creases, primarily in children in a few cases. Recall of skin reaction due to prior radiotherapy has occurred with Adriamycin administration.

Gastrointestinal—Acute nausea and vomiting occurs frequently and may be severe. This may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) may occur 5-10 days after administration. The effect may be severe leading to ulceration and represent a site of origin for severe infections. The incidence and severity of mucositis is greater with the 3 successive daily dosage regimen. Anorexia and diarrhea have been occasionally reported.

Vascular—Phlebosclerosis has been reported especially when small veins are used or a single vein is used for repeated administration. Facial flushing may occur if the injection is given too rapidly.

Local—Severe cellulitis, vesication and tissue necrosis will occur if Adriamycin is extravasated during administration. Erythematous streaking along the vein proximal to the site of the injection has been reported.

Hypersensitivity—Fever, chills and urticaria have been reported occasionally. Anaphylaxis may occur. A case of apparent cross sensitivity to lincomycin has been reported.

Other—Conjunctivitis and lacrimation occur rarely.

DOSAGE AND ADMINISTRATION

The recommended dosage schedule is 60-75 mg/square meter of body surface, as a single intravenous injection administered at 21-day intervals. The lower dose should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. An alternative dose schedule is 30 mg/square meter of body surface on each of three successive days repeated every 4 weeks. If hepatic function is impaired, Adriamycin dosage must be reduced according to the following table:

Serum Bilirubin Levels	BSP Retention	Recommended Dose
1.2 – 3.0 mg %	9 – 15%	½ normal dose
>3 mg %	>15%	¼ normal dose

Preparation of Solution: Adriamycin should be reconstituted with Sodium Chloride Injection U.S.P. as indicated in the Dilution Table.

Dilution Table		
Vial Size	Quantity of Diluent to be Added	Approximate Concentration
10 mg	5 ml	2 mg/ml
50 mg	25 ml	2 mg/ml

If Adriamycin powder or solution contacts the skin or mucosae, wash thoroughly with soap and water.

After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 24 hours at room temperature and 48 hours under refrigeration (4-10°C). It should be protected from exposure to sunlight and any unused solution should be discarded.

It is recommended that Adriamycin be administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection U.S.P. or five percent (5%) Dextrose Injection U.S.P. This procedure will reduce likelihood of extravasation and consequent tissue damage.

Adriamycin should not be mixed with heparin since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Until specific compatibility data is available, it is not recommended that Adriamycin be mixed with other drugs.

Adriamycin has been used in combination with other approved chemotherapeutic agents. Though evidence is available that at least in some types of neoplastic disease combination chemotherapy is superior to single agents, the benefits and risks of such therapy have not yet been fully elucidated.

HOW SUPPLIED

ADRIAMYCIN™ (doxorubicin hydrochloride) for injection is available in two sizes:

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Cardiac Output Measurement by Thermal Dilution

Reproducibility and Comparison with the Dye-Dilution Technique

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Cardiac output estimates by the principle of thermodilution (CO_{th}) was compared with dye-dilution estimates (CO_{dye}) in pigs. For CO_{th} estimates a Swan-Ganz 7 F floating thermodilution catheter and a 9500 Edwards Computer®, were used. The CO_{dye} estimates were obtained by the apparatus constructed by Zijlstra and Mook. The effect of the thermistor position in the pulmonary artery on the CO_{th} estimates was also investigated. The reproducibility of CO_{th} was examined by duplicate determinations. Based on 101 simultaneous estimates of CO_{th} and CO_{dye} the correlation was found $CO_{th} = 1.020\ CO_{dye} + 0.2378$, $r = 0.971$ for cardiac outputs between 0.65 l/min and 11 l/min. For 111 duplicate determinations of CO_{th} between 2 and 9 l/min the coefficient of variation was 4.74%. The thermistor position in the pulmonary artery had no influence on the CO_{th} estimates provided an undamped pressure curve could be monitored from the tip of the catheter. Cardiac output can thus be measured rapidly with good accuracy also for low values by means of a blindly inserted thermistor catheter positioned without x-ray control and a computer with digital display.

KNOWLEDGE of the cardiac output is useful in monitoring the circulation of the critically ill patient, especially if repeated information can be obtained speedily and easily, causing the least possible interference with treatment or nursing of the patient. In this laboratory the dye-dilution technique (CO_{dye}) has been used for the past 10 years. The accuracy and reproducibility of this method is well known[9,15,17,18] and for a long time it has been accepted as a method of reference as reliable as the Fick method over a wide range of clinical conditions.[14] It is however rather laborious, requires insertion of an arterial catheter and is not very accurate at low output stages.[17] Measurement of cardiac output by thermal dilution (CO_{th}) is easy to perform and can be repeated almost without limitations at very short intervals. This is especially so when the floating Swan-Ganz thermodilution catheter is used in combination with a cardiac output computer. The catheter allows injection of the cold charge as well as registration of the subsequent temperature changes in the pulmonary artery. The computer presents the cardiac output figure in less than 40 seconds, thus allowing one determination per minute. The purpose of this report is to determine the reproducibility of the CO_{th} estimates, to investigate the extend to which the site of the thermistor in the pulmonary artery affects the estimates and to determine the measure of agreement between CO_{dye} and CO_{th}. Several reports deal with the agreement of the two methods[1,6,13] they are however mainly concerned with the agreement in the normal and high ranges. As cardiac output estimates in the clinic are often of special interest at low output stages, when errors of measurement for CO_{dye} as mentioned are considerable, the present experimental study was designed to deal also with comparison of the two methods at low outputs.

Method

The thermodilution principle as introduced by Fegler[2-4] is based on the injection of a quantified cold charge and registration of its dilution i.e. the subsequent change in temperature of the blood at a point further on in the direction of the blood stream. As heat unlike dye will mix well irrespective of laminar flow in the blood vessels, the thermoindicator can be injected into the right atrium and the temperature registered in the pulmonary artery. From the area under the recorded dilution curve CO_{th} is

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derived according to the *Steward-Hamilton* equation[8] modified to calculate cardiac output by thermodilution.

$$CO_{th} = \frac{V_I \cdot (T_B - T_I) \cdot S_I \cdot C_I \cdot K \cdot 60}{S_B \cdot C_B \cdot \int_0^\infty \Delta T_B(t)dt} \qquad (1)$$

where V_I is the volume of injectate in ml; T_B and T_I are the temperatures of the blood in the right atrium and of the injectate arriving into the blood stream, respectively. S_B and S_I are specific gravity, C_B and C_I specific heat of respectively blood and injectate. When 5% dextrose is used as indicator we have:

$$\frac{S_I \cdot C_I}{S_B \cdot C_B} = 1.08$$

For the loss of indicator by transit of the cold solution through the catheter into the right atrium a correction factor is introduced:

$$K = \frac{T_b - T_m}{T_b - T_I}$$

where T_b is blood temperature, T_m is the mean temperature of indicator leaving the catheter tip and T_I the temperature of injectate immediately prior to injection. For the present Swan-Ganz® 7 F catheter, according to the manufacturer* K = 0,827, when 10 ml of 5% dextrose at 0 C is injected rapidly into the catheter. K has been found almost independent of injection time and the length of the catheter placed intravascularly.[5] When the known values have been inserted in equation (1), we have:

$$CO_{th} = \frac{10 \cdot 1.08 \cdot (T_B - T_I) \cdot 0.827 \cdot 60}{\int_0^\infty \Delta T_B(t)dt} \qquad (2)$$

or

$$CO_{th} = \frac{53.6 \cdot (T_B - T_I)}{\int_0^\infty \Delta T_B(t)dt} \qquad (3)$$

From this equation cardiac output is calculated by a small battery driven computer* by digital display showing the actual cardiac output between 1.5 1 and 10 1 per minute. A thermodilution curve also can be recorded from the computer; this was done by a Servograph®. The value 53.6, called the computation factor, is fed into the computer, and corresponds to a constant voltage in the computer, not to be changed unless the factor is changed. As there are certain limits to the size of the values the computer can handle, the computation factor must be altered for very low and for very high outputs. For CO_{th} lower than 1.5 1 the computation factor has to be increased by 3/2 and the computed CO_{th} accordingly to be multiplied by 2/3 to give the actual CO_{th}, conversely for cardiac outputs higher than 10 1 the computation factor must be reduced by 2/3 and the computed output consequently multiplied by 3/2. With the computation factor set, it will be necessary before each measurement only to feed the computer with the temperature difference between blood and indicator, and the desired computation time. This can be varied at intervals of 5 sec between 5–35 sec, and is adjusted to include the downslope of the recorded temperature curve just beyond the point where it becomes indistinguishable from the base line.

As a thermo-indicator was used 10 ml 5% dextrose injected at a temperature between 0 C and 2 C. Tricarbocyanin (Cardiogreen^R) was used as a dye-indicator, the dye-curve being registered by the apparatus of Zijlstra and Mook.[19] Through the thermodilution catheter 0.2 ml of the dye was injected into the right atrium, the cold charge being used to flush the catheter. Blood for registration of the dye curve was continuously sampled at a rate of 0.4 ml per second from a catheter in the carotid artery. CO_{dye} was calculated by planimetry of the dye-dilution curve. As to the part of the investigation concerned with the influence of catheter position on the CO_{th} estimate an electromagnetic square-wave flowmeter (Nycotron^R) was employed to ensure a constant cardiac output while CO_{th} measurements were carried out with the catheter in different positions.

Procedure

Eight pigs weighing from 68 kg to 72 kg were anesthetized with halothane and nitrous oxide. After injection of d-tubocurachloride intubation was carried out and they were ventilated with a Bird^R ventilator. With the animal in supine position the neck vessels were exposed on the right side. A Swan-Ganz 7 F catheter was introduced under pressure registration through the jugular vein to the pulmonary artery. For arterial sampling and pressure recording a catheter was introduced into the carotid artery. The neck incision was closed, leaving approximately 60 cm of the Swan-Ganz catheter intracorporally. Rectal temperature was considered representative for the blood temperature. The reproducibility of the thermodilution estimates was determined on two of the pigs. A preliminary CO_{th} estimate was carried out to allow determination of the optimal computation time from the length of the recorded thermo-dilution curve. Double determinations were then carried out within less than 2 minutes. During the few seconds of manual indicator injection the ventilator was stopped and the animals were apneic. To prevent cold indicator loss to the catheter, withdrawal of 1 ml blood into the syringe immediately succeeded the injection. After determination of the basal cardiac outputs the pigs were hypo-ventilated and the ensuing rising outputs were recorded. Under following normoventilation the animals were subsequently bled slowly into hypovolaemic shock, while the declining outputs were recorded. On the assumption that errors of method and instrumentation are normally distributed the variance is calculated as:

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* Edwards Laboratories: The Edslab. Thermodilution catheter and 9500 Edwards cardiac output computer.

$$S^2 = \frac{1}{2n} \cdot \sum_{1}^{n} d^2,$$

where d is the difference between two double estimates and n is the number of observations. The *t-test* for pair samples was applied to assess the significance of any difference between first and second measurement.

Simultaneous CO_{th} and CO_{dye} estimates were carried out in 4 pigs prepared as described above. Injections of both indicators together were made manually in less than 5 seconds. In order to investigate whether the site of the thermistor in the pulmonary artery influenzed the CO_{th} estimates, median sternotomy was performed in two pigs and an 18 mm electromagnetic flow probe (Nycotrom^R) was fitted around the pulmonary trunk. Pulmonary artery flow was recorded in order to ascertain a stable cardiac output during measurements with the cathether in two different positions. Due to difficulties in obtaining a zero reading for a flow probe on the pulmonary artery absolute values have not been considered for the electromagnetic measurements. Initially the extend to which the catheter influenzed the electromagnetic field was studied. Then during constant pulmonary artery flow CO_{th} was measured first with the tip of the Swan-Ganz catheter in the pulmonary trunk controlled by digital palpation, then with the tip advanced to the most peripheral position allowing an undamped pulmonary artery pressure curve to be recorded. The difference between the two positions of the catheter was approximately 8 cm. All determinations were duplicate. These measurements were also carried out at different levels of cardiac output obtained as above described by hypoventilation and slow bleeding respectively.

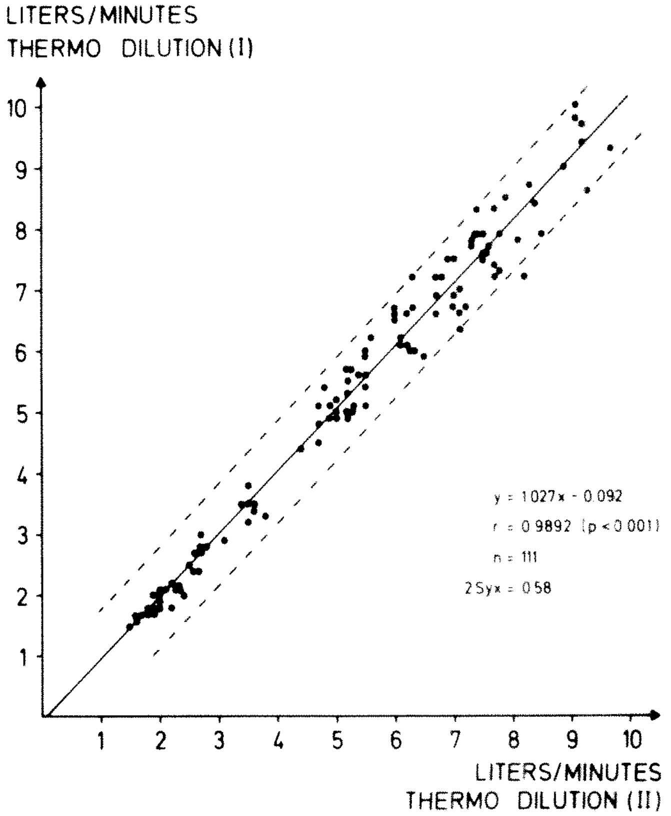

FIG. 1. The reproducibility of CO_{th} estimates in pigs. 111 double estimates, each set performed within 2 minutes.

Results

For 111 double determinations of CO_{th} no significant difference was found between the first and the second measurement completed within 2 minutes from the first injection (Fig. 1). The material has been divided into 6 subgroups according to the size of CO. As seen from Table 1 the coefficient of variation between measurements does not exceed 5.45% in any of the subgroups and for the whole series amounts to 4.74%. Correspondingly the 99% confidence limit does not exceed 10.6% for CO_{th} between 2 l/min and 9 l/min. Whether or not the Swan-Ganz catheter interfered with the elec-

TABLE 1. *Reproducibility of Cardiac Output (CO) Determination Calculated from 111 Double Measurements*

CO (l/min)	n	$\bar{x}$	s	$\frac{s \cdot 100}{\bar{x}}$	95% limit liter	95% limit % of $\bar{x}$	99% limit liter	99% limit % of $\bar{x}$
1.5–2.99	29	2.17	0.1181	5.45	0.1708	7.9	0.2302	10.6
3.00–4.99	14	4.13	0.1627	3.94	0.2468	6.0	0.3425	8.3
5.00–5.99	18	5.35	0.2355	4.40	0.3498	6.5	0.4793	9.0
6.00–6.99	19	6.53	0.2911	4.46	0.4308	6.6	0.5889	9.0
7.00–7.99	21	7.63	0.2977	3.90	0.4378	5.7	0.5960	7.8
8.00–10.01	10	9.00	0.3788	4.20	0.5968	6.6	0.8489	9.4
All CO	111	5.32	0.2526	4.74	0.3539	6.7	0.4601	8.6

Number of observations (n). Standard deviation of the mean (s). Coefficient of variation $\frac{s \cdot 100}{\bar{x}}$ · 99 per cent limit $\left(\frac{s}{\sqrt{2}} \cdot t_n\right)$.

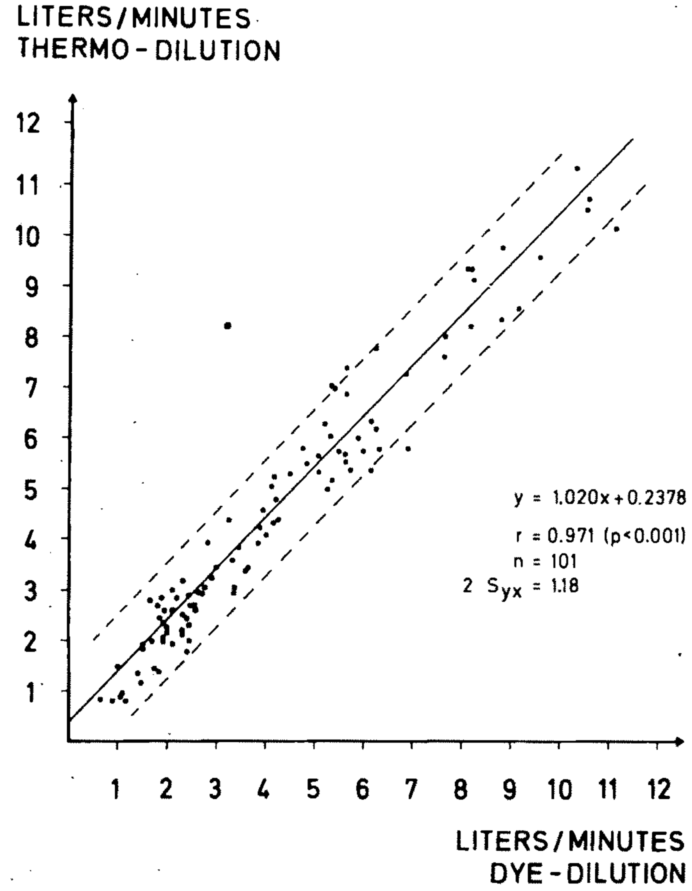

FIG. 2. Simultaneous CO_{th} and CO_{dye} estimates in pigs. The results of 101 measurements.

tromagnetic measurements was examined for flows ranging from 0.84 l/min to 8.16 l/min, 18 sets of measurements were carried out, each comprising duplicate determinations with, respectively without the catheter under the flow probe. The difference was 0.118 l/min ranging from + 0.256 l/min to − 0.030 l/min ($P > 0.05$). Thus no significant difference could be demonstrated between electromagnetic flow measurements with and without the catheter under the flow probe.

To test whether the site of the thermistor in the pulmonary artery affects the estimation of CO_{th}, 21 sets of CO_{th} measurements were taken of flows ranging from 1.46 l/min to 6.31 l/min as measured by the electromagnetic flowmeter. Each set of measurements comprised duplicate determinations of CO_{th} and electromagnetic flow with the catheter tip in the pulmonary trunk (CO_{th} central) as well as peripherally (CO_{th} peripheral) in the artery respectively. No significant change in cardiac output took place between measurements of CO_{th} with the catheter in the two different positions. The difference CO_{th} peripheral-CO_{th} central between the mean values of the duplicate thermal dilution determinations was 105 ml, ranging from +210 ml to −420 ml ($P > 0.05$). Thus no significant differences could be demonstrated between CO_{th} determined with the catheter in a central and in a peripheral position in the pulmonary artery, provided an undamped pulmonary artery pressure curve was observed.

The CO_{th} and CO_{dye} estimates were compared from 101 simultaneous measurements carried out on 4 pigs with 15 to 35 determinations for each animal. Cardiac outputs expressed as CO_{th} ranged from 0.65 l/min to 11.4 l/min (Fig. 2). Linear regression analysis yielded the equation: $CO_{th} = 1.020\ CO_{dye} + 0.2378$. The coefficient of correlation between the two estimates was $r = 0.971$. The intersection of the regression line on the Y-axis (CO_{th}) seems to differ from zero ($0.02 < P < 0.05$). The mean values of the estimates were $CO_{th} = 4.519$ l/min and $CO_{dye} = 4.198$ l/min respectively, the mean difference being $CO_{th} - CO_{dye} = 0.321$ l/min (SD = 0.056). For cardiac outputs about 4 l/min. CO_{th} is thus estimated 7.7% higher than is CO_{dye}.

Discussion

The great advantages of the thermal dilution method over other methods for estimation of the cardiac output are the simplicity of the operational procedure, the almost unlimited number of observations allowed and especially compared with the dye-dilution technique, that no arterial catheter is needed.

Loss of the indicator outside the blood stream constitute the most serious error of the thermal dilution technique. The correction factor $C = 0.827$ implies that about 17% of the cold charge of 10 ml 5% glucose at 0 C will be lost under optimal conditions before the injectate leaves the catheter. Any delay in handling the syringe after its removal from the ice water bath will increase the extracorporeal indicator loss unaccountably. Such risks may be avoided by injecting the indicator at room temperature. This however decreases the sensitivity of the method by 2–3 times, necessitating a corresponding increase in volume of the injectate.[16] Included in the indicator loss corrected for is the amount contained in the catheter at the end of the injection and subsequently removed by withdrawal of blood into the catheter. Leaving the injectate in the catheter causes additional cooling of the blood by conduction across the wall of the catheter. The time lag before equilibrium has been reached between blood and catheter will delay the return of the downslope of the thermal curve to the base line, resulting in an ill-defined tail.

The temperature of pulmonary artery blood shows variations with the heart rate as well as with the respiratory rate. Especially frequencies in the respiratory range are clearly seen on the base line during work and may well make the interpretation of a baseline for calculation of the dilution area more difficult. Olsson et al.[10] stress the importance of a steady state including avoidance of movements and deep-breaths. They also point out that the return of cold venous blood resulting from raising of an extremity may give a decrease in temperature of the pulmonary artery blood of the same order of magnitude as the thermodilution curve itself. A more stable base line is obtained if thermal dilution is registered from the aorta. On the other hand highly unreliable estimates will result if the thermal indicator has to traverse pathological lungs as pointed out by Pavek et al.[11] The particular influence of all these possible sources of error can be estimated only in well controlled model experiments from which on the other hand little can be deducted about their combined effect on the accuracy and reproducibility of the CO_{th}-estimates under clinical conditions.

In the surgical clinic the main indication for repeated cardiac output estimates will be low and/or unstable output states in the severely ill patient or the patient subjected to major surgery. The experimental condition of this study answers well to this description. It should be especially noted that cardiac output, except for the basal values, were too unstable both under hypoventilation and bleeding of the animal to allow an evaluation of the reproducibility of the dye dilution method which requires steady state for well defined 5 minute periods.

With a coefficient of variation not exceeding 5.45% for outputs down to 1.5 l/min, the reproducibility of the thermal dilution estimates in animals of approximately 70 kg compares favorably with clinical results obtained by the dye dilution method. Wiberg-Jørgensen et al.[17] found thus, in a series of patients subjected to cardiac surgery, during steady states, coefficients of variations for double dye estimates between 7 and 26% corresponding to cardiac indices between 4.0 and 0.92.

It is of great importance for the clinical use of the method that no significant difference could be demonstrated between thermal dilution estimates obtained with the catheter in the pulmonary trunk and with the catheter as far out in the artery for an undamped pressure curve still to be obtained.

The simultaneous thermal and dye-dilution estimates showed a good correlation between the two methods over a wide range of outputs from 0.65 l/min to 11.4 l/min. Cardiac output determined by thermal dilution is however higher than by the dye method. The equal distribution of observations over the whole range covered allows the difference to be expressed as the difference between mean values. This calculated CO_{th} yields 7.7% higher values than does CO_{dye}. This is in accordance with the observation of Jose et al.[7] and Rahimtoola and Swan[12] who in normal subjects found cardiac output determined 7% higher with left atrial or left ventricular injection than with pulmonary artery injection. Also Wiberg-Jørgensen et al.[17] found cardiac output underestimated by 5% using right atrial injection compared with estimates from left-sided injection during operations for valvular disease. As discussed by these authors the underestimation in right sided injection is due to the early recirculation of dye particles from the coronary circulation.

Though inference between clinical and experimental series should be drawn with caution, it seems reasonable to conclude that thermal dilution estimates of cardiac output are not only highly reproducible but also more accurate than estimates from dye-dilution curves in the lower flow ranges and during unstable flow conditions. Considering the nature of the dilution curves this should also be expected: whereas the dye curve becomes more flat and ill defined at low outputs, the thermal curve becomes steeper and covers a larger area, allowing a more accurate estimate either by computation or planimetry.

While a detailed analysis of methodological and instrumental errors of a thermal dilution system is hardly practicable in a clinical laboratory, the overall reliability of any commercial equipment should always be evaluated against an accepted reference method. If a thermodilution system compares favorably in the flow range best suited to the reference method it should offer advantages over other methods in low flow ranges.

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Mechanical Circulatory Assistance with Intra-aortic Balloon Counterpulsation for Major Abdominal Surgery

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Intra-aortic balloon counterpulsation (IABC) provides effective mechanical circulatory assistance (MCA) in many patients with cardiac disease characterized by low cardiac output and/or myocardial ischemia. The intra-aortic balloon pump (IABP) has been used almost exclusively in the care of patients with cardiac disease as their primary medical disorder. This report presents use of the IABP in three cases where cardiac disease was present, but abdominal pathology necessitating urgent surgical intervention was the primary medical concern. Experience with these three cases suggest that operative and early postoperative use of IABC in patients with documented heart disease undergoing major non-cardiac surgical procedures may reduce the high incidence of cardiac complications.

THE INTRA-AORTIC balloon pump (IABP) has proven an effective mechanical circulatory assistance (MCA) device in a variety of clinical conditions characterized by cardiogenic shock and/or myocardial ischemia.[5-7,10,13] Intra-aortic balloon counterpulsation (IABC) produces MCA by: 1) augmentation of arterial diastolic and coronary perfusion pressures, and 2) reduction of impedance to left ventricular ejection and heart work.[3,12,16] To date, the IABP has been used in patients with cardiac disease as their primary medical disorder. Recently, we have employed the AVCO-MGH intra-aortic balloon (IAB) system in 3 patients with known heart disease, but in whom the primary medical concern was abdominal pathology requiring urgent surgical intervention.

Case Reports

Case 1. A 57-year-old man sustained an acute myocardial infarction (MI) on 11/7/73. Congestive heart failure (CHF) developed following the MI; it was alleviated partially by administrating digoxin and diuretic preparations. At the time of discharge from the hospital on 11/20/73 he was in New York Heart Association (N.Y.H.A.) Class IV.

On 1/29/74 the man was readmitted to University Hospital for further evaluation. Physical examination revealed signs of biventricular heart failure. A non-tender large right flank mass was palpated. An electrocardiogram (ECG) showed a left anterior hemiblock and an old anteroseptal MI. At cardiac catheterization a discrete aneurysm occupying most of the anterior wall and apex of the left ventricle was visualized. The cardiac index (CI) was 1.4 L/min/m^2, with a left ventricular end diastolic pressure (LVEDP) of 24 mm Hg and a left ventricular ejection fraction (LVEF) of 13.5%. Other pressures recorded were: right atrium (RA)—7 mm Hg, pulmonary artery (PA)—47/27 mm Hg, and pulmonary artery occluded (PAo)—29 mm Hg. Visualization of the coronary arteries revealed a left dominant system with complete cut-off of the left anterior descending artery beyond the first septal perforator. The right and left circumflex coronary arteries had no significant disease.

Investigation of the flank mass indicated a right kidney hypernephroma without evidence of metastases.

It was decided that the patient's cardiac disease took precedence in therapy over his renal tumor since the markedly diminished cardiac function precluded nephrectomy. On 2/28/74 the left ventricular aneurysm was resected. At the completion of the resection, the patient could not be weaned from cardiopulmonary bypass (CPB) without the rapid development of left ventricular failure and cardiogenic shock. MCA with IABP was established and CPB could be discontinued. The postoperative course was complicated by CHF with low cardiac output (CO), renal and hepatic failure. After a slow recovery the patient was discharged on 4/6/74 with digoxin and diuretic medications.

On 7/2/74 the man was readmitted to undergo a right nephrectomy. He felt improved since the cardiac surgery, although clinically he remained in NYHA Class IV, the right flank mass remained non-tender, but had increased in size since his last hospitalization.

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TABLE 1. *Hemodynamic Data Noted in Case 1 On and Off IABC on Day of Surgery and First Postoperative Day*

	Blood Pressure (mm Hg)		Pulse beats/min	CVP (mm Hg)	PA (mm Hg)	CI L/min/m²
	Systolic	Diastolic				
Preop without IABC	100	70	100	20	55/20	1.64
Preop with IABC	90	110	88	18	45/20	1.86
1st postop day with IABC	95	110	95	8	35/20	2.10
1st postop day without IABC	100	75	100	10	40/20	1.78

Repeat investigation of this mass again indicated a right hypernephroma without evidence of distant metastases.

The decision was made to proceed with the nephrectomy, and to provide MCA with IABC during the surgery and early postoperative period because of the patient's reduced cardiac function. On 7/10/74 in the operating room under local infiltrative anesthesia, a brachial artery catheter, Swan-Ganz pulmonary artery catheter and IAB were placed. A satisfactory PAo could not be obtained for technical reasons. Hemodynamic parameters on and off IABC are presented in Table 1. With satisfactory MCA established, general endotracheal anesthesia was administered and an uncomplicated right nephrectomy performed. Total operating time was four hours.

Intraoperative hypotension did not develop, although the CI reached a low of 1.61 L/min/m², even with MCA. Postoperatively, MCA was continued for 24 hours, following which the patient was weaned from the IABP without the need of inotropic agents to maintain adequate tissue perfusion. Mild liver failure did develop early in the postoperative period, but no renal failure.

Pathologic examination of the surgical specimen revealed a renal cell carcinoma, clear cell type. The renal vein, artery, and ureter were free of tumor at the resection margins and no vascular invasion was identified. The man was discharged on 7/24/74 with digoxin and diuretic medications.

Case 2. An 88-year-old man was hospitalized on 7/11/74 with a 4 month history of angina, pedal edema and melena. He had had two prior episodes of rectal bleeding in 1966 and 1973. Diagnostic studies had revealed extensive diverticulosis of the colon. The patient was remarkably alert for his age. At age 21 years he had been told he had a heart murmur, but subsequently had not received specific cardiac therapy. He had had two syncopal episodes in the past 8 years.

Cardiovascular examination demonstrated signs of severe aortic stenosis without CHF. Abdominal examination revealed no abnormalities. Cardiac enlargement and calcium deposits in the aortic valve area were seen on the chest x-ray. The ECG showed sinus tachycardia, evidence of left ventricular hypertrophy and myocardial ischemia. An echocardiogram demonstrated a calcified aortic valve and a thick-walled left ventricle with a small cavity.

Investigation of the intestinal bleeding source again revealed extensive colonic diverticulosis.

Initial therapy included transfusions, digoxin and diuretics. The melena persisted and the patient required 32 units of blood during the first 21 days of hospitalization in order to maintain his hematocrit above 30%. Following an episode of increased rectal bleeding, an urgent colectomy was planned. On 8/1/74 the patient was taken to the operating room where under local infiltrative anesthesia a brachial artery catheter. Swan-Ganz pulmonary artery catheter and IAB were placed. MCA with IABC was employed during the induction of general anesthesia and surgery. A subtotal colectomy and splenectomy were performed. Total operating time was 4 hours. No hypotension developed during the operation. Postoperatively, IABC was continued for 24 hours, following which the patient was weaned from MCA without difficulty. No cardiac inotropic agents were required. The patient was discharged 17 days after operation.

As seen in Table 2, during the MCA period IABC produced two hemodynamic effects in this case: 1) the systolic arterial pressure was reduced (mean decrease 23 mm Hg), and 2) the diastolic arterial pressure was increased (mean rise 95 mm Hg) IABC produced no marked changes in left ventricular filling pressure (PAo) which were low (15 mm Hg) and no changes in cardiac indexes which were high (2.5L/min/m²).

Case 3. A 64-year-old woman was admitted on 11/5/74 for elective mitral valve replacement. The patient had received medical care for mitral valve disease for 10 years. Cardiovascular examination revealed CHF, cardiomegaly and murmurs consistent with mitral insufficiency and stenosis. An ECG demonstrated atrial fibrillation and a left bundle branch block pattern. Chest x-ray showed biventricular and left atrial enlargement. Clinically she was in NYHA Class IV. A past history of duodenal peptic ulcer disease which had responded to non-surgical management was elicited.

Cardiac catheterization revealed a dilated left ventricle with generalized hypokinesis and severe mitral regurgitation. The CI was 1.6 L/min/m², LVEDP—19 mm Hg, PAo—34 mm Hg, and PA—65/45 mm Hg. The effective mitral valve area was calculated at 1.0 cm². The right coronary artery was narrowed approximately 50% in its proximal course by atherosclerotic disease.

On 11/11/74 the patient underwent mitral valve replacement without serious incident. Low CO presented following surgery, despite the use of cardiac pressor agents. Peak CI recorded on the first postoperative day was 1.4 L/min/m². The patient became comatose with onset of liver and kidney failure. Melena was noted first on the sixth postoperative day; subsequently, guaiac positive material drained from the nasogastric tube. The bleeding source was presumed to be a duodenal

TABLE 2. *Hemodynamic Data Noted in Case 2 On and Off IABC on Day of Surgery and First Postoperative Day*

	Blood Pressure (mm Hg)		Pulse Beats/min	CVP (mm Hg)	PAo (mm Hg)	CI L/min/m²
	Systolic	Diastolic				
Day of Surgery without IABC	170	100	110	4	8	2.65
Day of Surgery with IABC	150	175	105	3	7	2.55
1st postop day with IABC	130	140	100	2	11	2.69
1st postop day without IABC	140	60	110	3	14	2.68

ulcer; although investigation, including an arteriogram, failed to reveal a definite site. Transfusion with 15 units of blood was required in the next 72 hours to maintain a hematocrit about 30%. Eight days following her cardiac surgery, the patient was returned to the operating room for an exploratory laparotomy because of the continued gastrointestinal hemorrhage. Although it was intended to provide MCA with IABC prior to beginning the abdominal procedure, the patient suffered a cardiac arrest as the femoral artery was being exposed under local infiltrative anesthesia. She was successfully resuscitated, and the abdomen opened as the AIB insertion was completed. After cardiac resuscitation her blood pressure (BP) prior to IABC was 90/55 mm Hg; with IABC the BP rose to 70/110 mm Hg. At laparotomy a bleeding duodenal ulcer was found and oversewn. A vagotomy and pyloroplasty was performed. The operating time was 3 hours.

Following abdominal surgery MCA was maintained for 48 hours. Although no CO determinations were obtained during this period and a minimal isoproterenol infusion continued, it was observed that with IABC the BP ranged from 90/100 to 120/140 mm Hg; off IABC the BP ranged from 100/60 to 120/70 mm Hg. The isoproterenol infusion was continued for 24 hours after discontinuing IABC; thereafter, no further cardiac support was required. No ECG evidence of intra or postoperative MI was found. The patient died in renal failure on 12/10/74.

Discussion

An operative mortality statistic based on experience gained from a group of patients undergoing a specified surgical procedure often does not reflect accurately the individual patient's risk. From literature reporting on large series of cases, the operative mortality associated with a nephrectomy for renal cell cancer is 1%, and that associated with the urgent colectomy due to bleeding from diverticular disease is 10%.[8,11] An overall mortality of 6 to 9% can be expected in emergency surgery for duodenal peptic ulcer disease, depending upon the type of procedure performed.[3] We believe that the operative risks for the 3 patients presented far exceeded the group figures quoted because of their cardiac status. Clinically, there is a little doubt that heart disease enhances the danger of any abdominal operation although good statistics are not available to define precisely the added risks for specific cardiac disorders.

An increase in morbidity and mortality among patients with coronary artery disease undergoing general anesthesia has been reported, with the risk enhanced by the occurrence of a MI 6 months or less preoperatively.[1,9,14,15] The mortality among patients who have had a preoperative MI and suffer a recurrent MI intra or postoperatively is estimated to range between 40 and 70%. Mauney and associates[9] have reported on the incidence of perioperative MI in a prospective study of 365 patients over the age of 50 years undergoing major non-cardiac operations with one or more of the following preoperative ECG abnormalities: 1) previous MI; 2) bundle branch block; 3) left ventricular strain or hypertrophy; or 4) ST segment signs of subendocardial injury. Thirty patients (8%) in this group had a perioperative MI, with 16 (53%) dying as a result of the MI. The risk of death due to postoperative MI for the whole group was 4.4%. A direct correlation was found between the incidence of postoperative MI and both the length of the operative procedure and incidence of intraoperative hypotension.

Augmentation of systemic diastolic pressure, a reflection of coronary artery perfusion pressure; and reduction of systemic systolic pressure, a reflection of heart work, were witnessed with IABC in the three cases presented. These beneficial hemodynamic effects were particularly impressive in Case Two (Table 2). In the two patients who had determinations made, IABC either maintained (Case 2) or increased (Case 1) CO at reduced heart work levels. MCA with the IABP for their abdominal surgical procedure aided in the prevention of hypotension in our three patients. Avoidance of hypotension is necessary to prevent MI, particularly in patients with coronary artery disease and aortic stenosis with left ventricular hypertrophy.

By raising coronary perfusion pressure nd reducing heart work MCA with the IABP may increase myocardial nutrient supply and decrease myocardial nutrient demand. This effect can be especially important in areas of the myocardium that have marginal perfusion. In contrast, attempts to support a failing circulation by administering pharmacological agents with cardiac inotropic effect, e.g. isproterenol, will produce little or no improvement of coronary perfusion and may greatly increase myocardial nutrient demand. Of the three cases presented, only the third required pharmacological aid for circulatory support in addition to IABC at the time of the abdominal surgery. Postoperative ECGs showed no evidence of MI in any of the patients.

Our three patients were not anticoagulated and received only low molecular weight dextran (10 cc/hr) during IABC. Thromboembolic complications were not encountered. Some authors recommend routine heparin anticoagulation during IABC. In our experience with balloon counterpulsation in 78 patients, anticoagulation with heparin was used in 38. In the remaining 40 patients we felt that anticoagulation was contraindicated because of concurrent major surgical procedures or early postoperative state. In the latter group only LMWD was used. Thromboembolic complications were minimal in the entire series and no difference was observed whether heparin was given or not. Based on this experience it is our distinct impression that anticoagulation, a potential limiting factor during a surgical procedure, is not necessary for IABC.

Morbidity resulting from the use of the IABP has been low, with the few serious complications relating to lower limb ischemia secondary to femoral artery trauma at the balloon insertion site. Mortality attributable to the IABP is rare, with only one death reported as the result of balloon rupture.[3–5,13,16] We believe the risks involved in the use of the IABP are far outweighed by the benefits provided by MCA with IABC in properly selected cases.

The usefulness of IABC in cardiogenic shock of various etiologies has been relatively well defined. In addition we have used IABC in septic shock with some success.[2] The employment of MCA with IABP during noncardiac operations in patients with far advanced heart disease is a novel approach. In this situation IABC appears an attractive modality since it provides a more physiologic support of the left ventricle, without undesirable side effects, than the commonly employed inotropic drugs. Thus it seems that balloon counterpulsation merits more extensive application. However, the specific indications for its use remain to be delineated pending additional experience. At the present time we feel that IABC may be beneficial in patients with advanced heart disease (NYHA Classes III and IV) from any cause who are subjected to major surgical procedures. In addition patients who need life saving noncardiac operations during unstable angina pectoris or within 6 weeks of a transmural myocardial infarction should be considered for MCA with IABP. This clinical application of the IABP may reduce the cardiac morbidity and even mortality in this group of patients, and deserves further evaluation.

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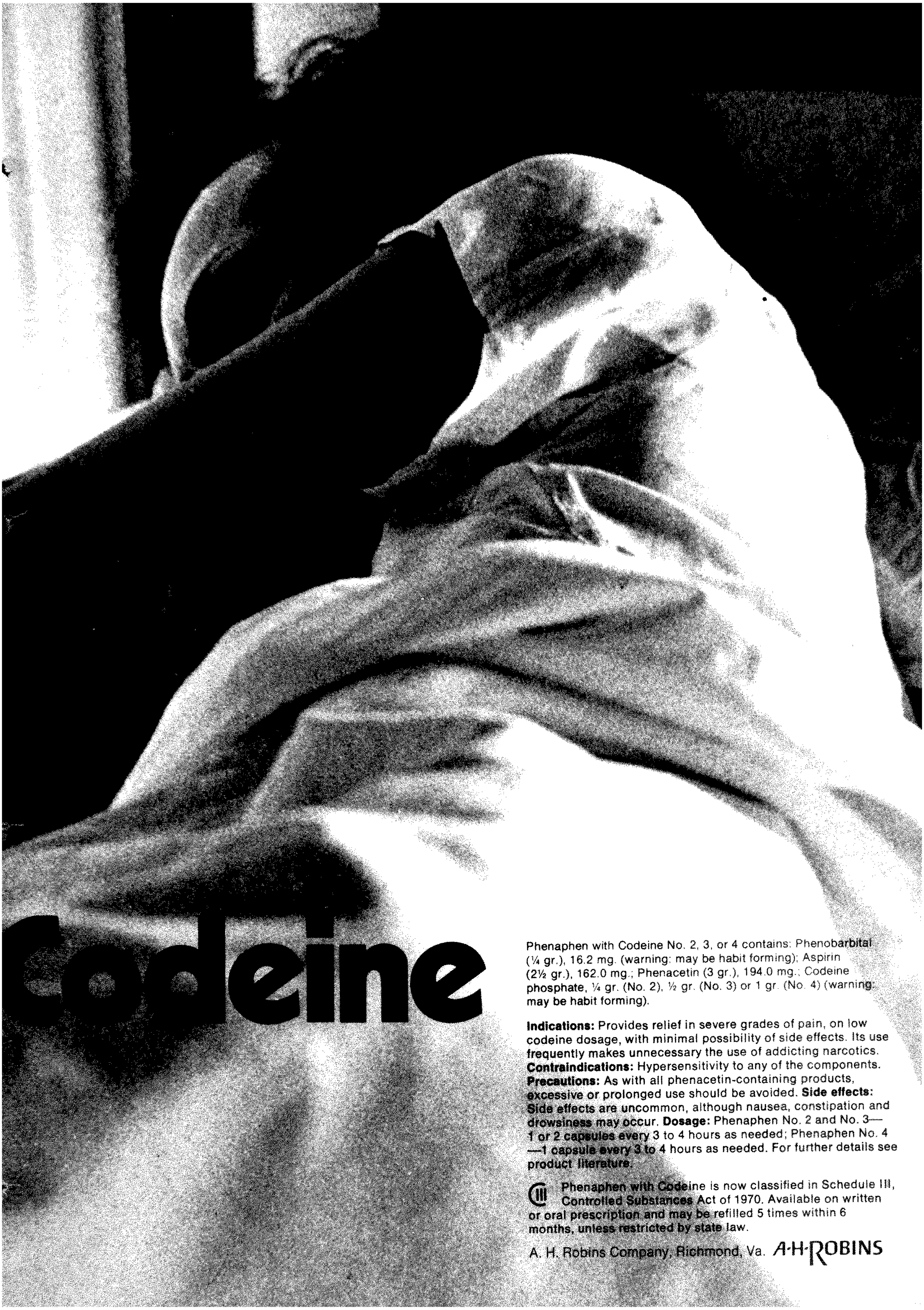

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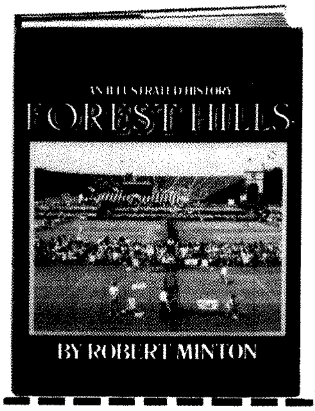

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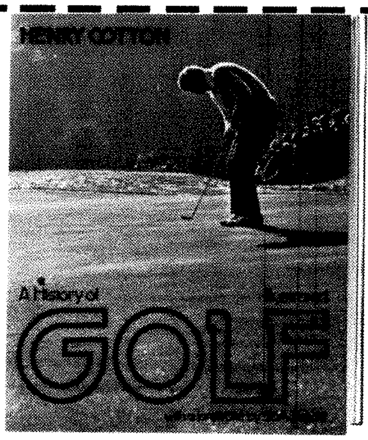

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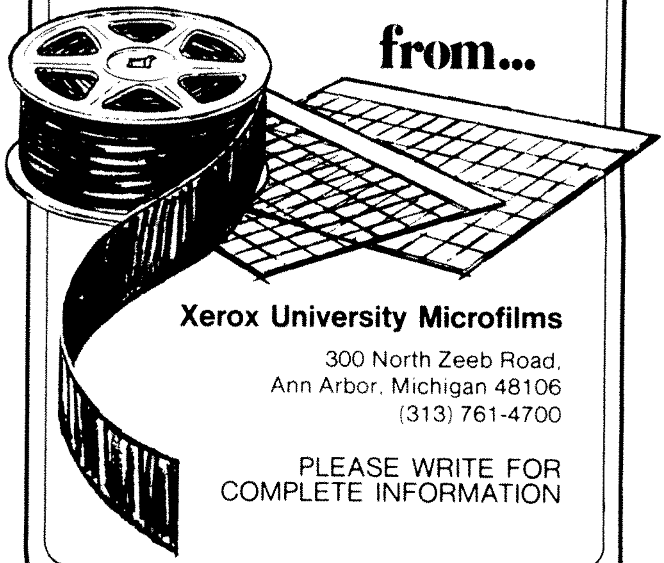

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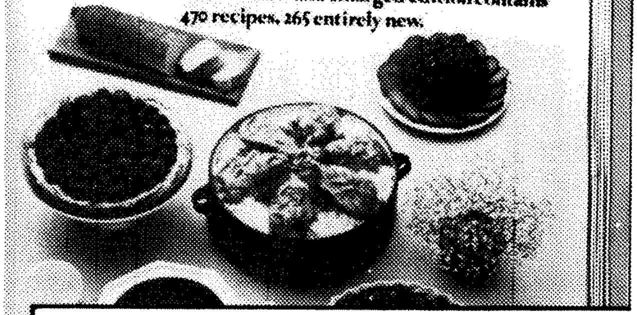

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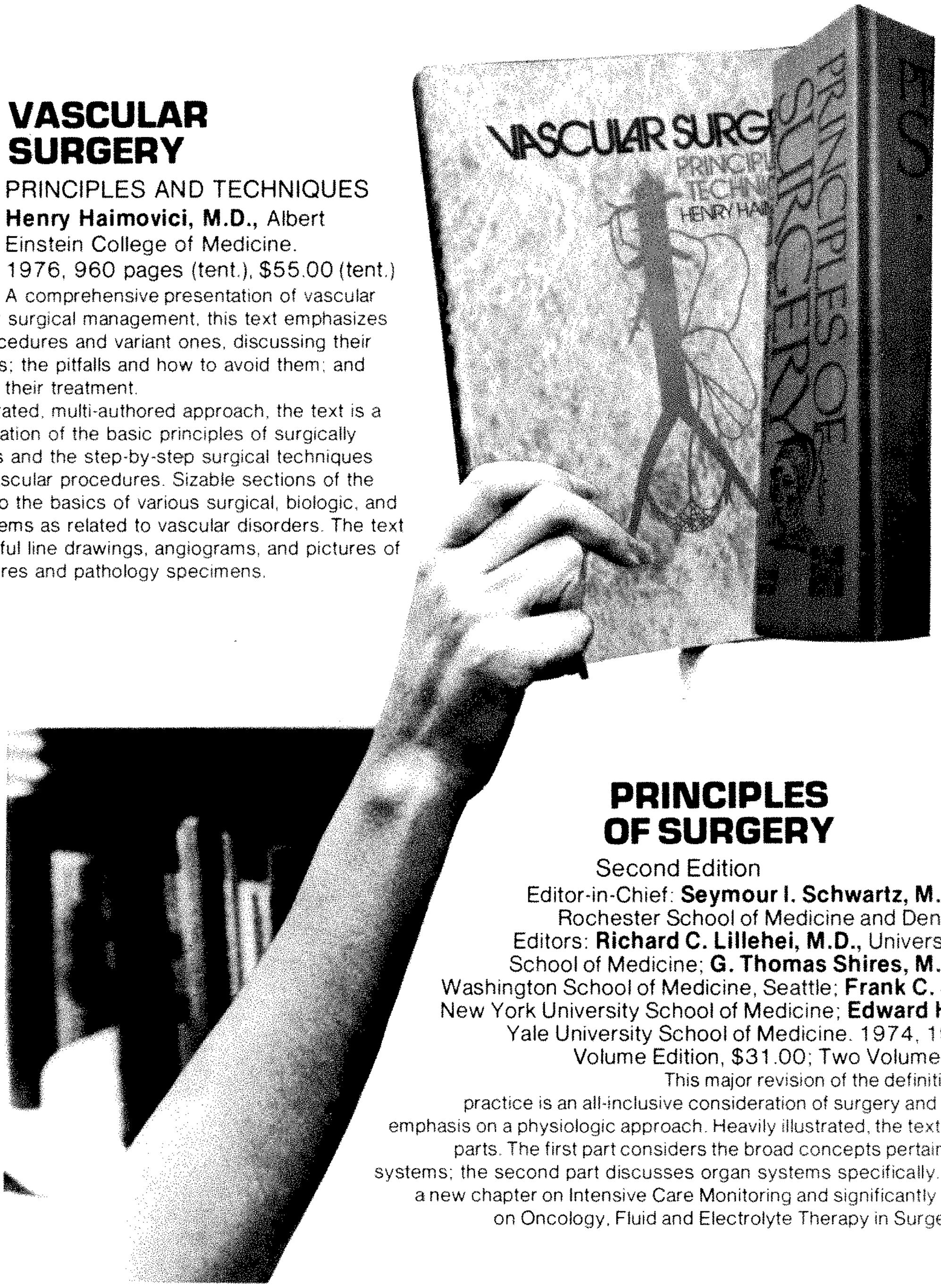

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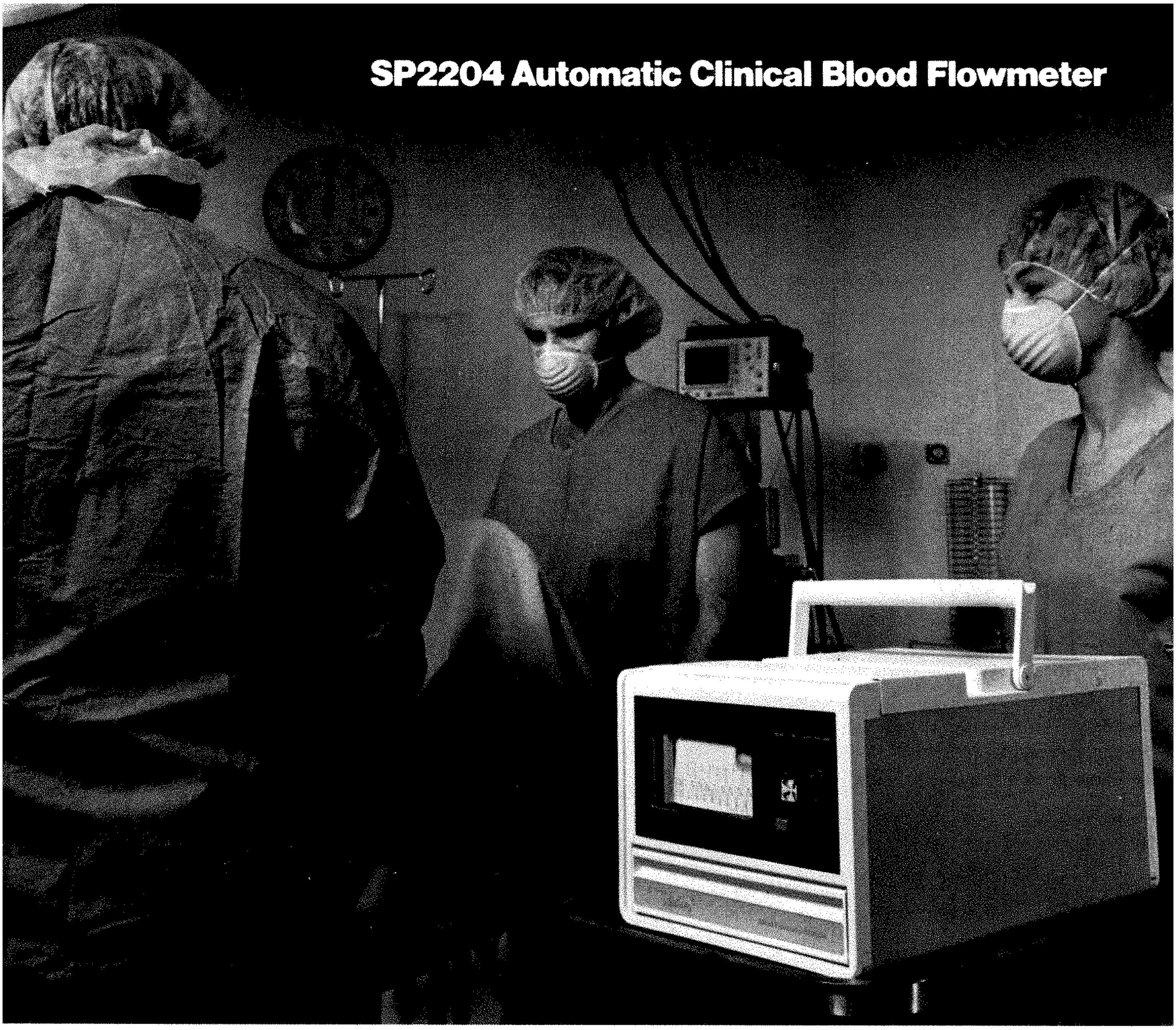

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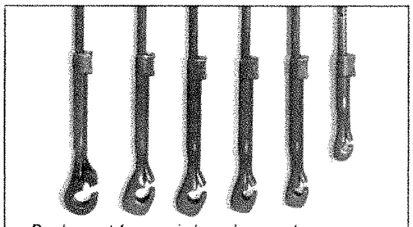

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Acute Colitis in the Renal Allograft Recipient

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Four renal allograft recipients with evidence of ischemic damage to the colon are presented and compared with 11 cases from 5 major series. Similarities in the patients included: deterioration of renal function, multiple immunosuppressive and antibiotic regimens, the use of cadaver renal allografts, and diagnostic and therapeutic measures requiring frequent enemas with barium and ion-exchange resins. Two of our patients underwent surgery for the removal of segments of necrotic colon after several weeks of fever and abdominal pain initially attributed to either acute rejection, viral infection, or pancreatitis. One patient had three days of melena and responded to non-operative therapy. The fourth patient developed ischemic colonic changes 10 weeks after allograft nephrectomy and was receiving no immunosuppression at the time. Broad spectrum antibiotics were used at various times in all patients. Early aggressive evaluation of gastrointestinal complaints—including barium enema, upper gastrointestinal series with small bowel follow-through, proctosigmoidoscopy or colonoscopy, and arteriography—is indicated, in view of the lethality of the complication of colonic ulceration. The clinical pictures presented emphasize the fact that recipients of renal allografts are commonly heir to many complications which may be considered rare in the normal population.

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ISCHEMIC COLITIS is a self-limited phenomenon characterized by compromise of the circulation to the colon in patients with atherosclerotic narrowing of the superior and inferior mesenteric arteries and their branches. The patients are usually in the sixth or seventh decades and their clinical courses include one or more of three transitional patterns as originally described by Boley et al.[7] and expanded by Marston and co-workers[21] i.e.: 1) abdominal angina; 2) reversible ischemic colitis; and 3) in extreme cases, gangrenous enterocolitis.

Pathologic findings vary from the mucosal pallor often seen in patients with intestinal angina to the full-thickness loss of mucosa with ulceration, hemorrhage and stricture seen in ischemic colitis. In addition, some patients develop frank colonic infarction and gangrene. The most commonly described areas of involvement have been the left transverse colon, splenic flexure and descending colon with sparing of the rectum; however, more recent reports describe involvement of the rectum, especially in cases occurring after surgery on the abdominal aorta.[5,15,16,26]

The radiologic features include five characteristic signs on barium enema and plane films of the abdomen. These are: 1) "thumb-printing," thought to be indicative of reversible smooth muscle defects due to hemorrhage into the bowel wall; 2) "saw-tooth" irregularity of the mucosa, characteristic of mucosal ulceration; 3) tubular narrowing; 4) sacculation of the involved segment of the colon, indicative of stricture formation; and 5) pseudopolypoid filling defects, which are attributed to remaining areas of normal mucosa following partial slough of necrotic mucosa.[21]

This report reviews the clinical courses of four recipients of cadaver renal allografts, all of whom demonstrate diagnostic and pathologic features similar to those of ischemic colitis. The roles of immunosuppression, opportunistic infection, and retroperitoneal surgery, as contributing factors in the development of the colonic lesions, will be considered and a review of 11 cases in the literature follows the case reports.

Case Reports

Case 1. H. H., a 45-year-old Caucasian man, underwent bilateral nephrectomy and cadaver renal allotransplantation on 7/21/72. The kidney was placed in the right iliac fossa with an end-to-end anastomosis of the renal to hypogastric artery and an end-to-end side anastomosis of the renal to external iliac vein. In the first eighteen hours postoperatively 3800 ml of urine were produced. On the sixth, seventh and

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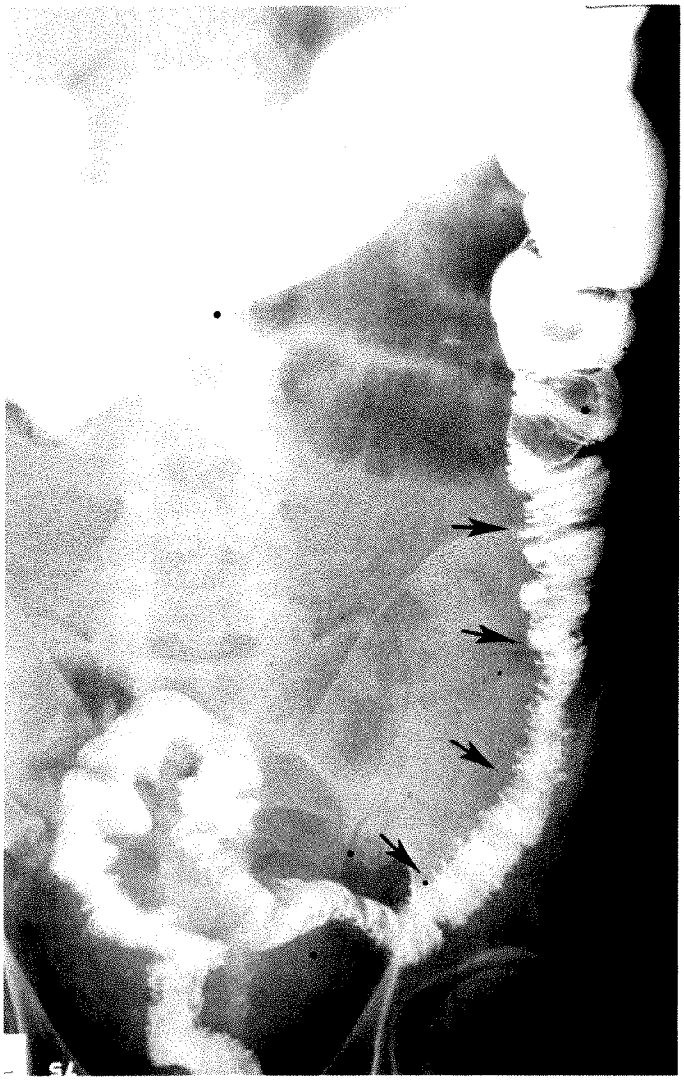

FIG. 1. Barium enema examination, Patient 1. There is edema and marked irritability of the descending colon and sigmoid colon (arrows).

eighth postoperative days, he received, in addition to the routine immunosuppression with oral prednisone and azathioprine, one gram per day of intravenous methylprednisolone for acute rejection and began oral oxacillin for a staphylococcal wound infection. During the third week post-transplantation he developed left lower quadrant pain and vomiting, and serum amylase was 516 units (N = 40 – 180). Intravenous fluid and electrolyte support were instituted, and renal function remained stable with serum creatinine 1.5 mg%. A reduction in the azathioprine dose from 150 mg to 50 mg daily was necessitated by leukopenia (2,500–3,000/mm^3). Abdominal symptoms continued, and during the fifth postoperative week, a barium enema showed spasticity and narrowing of the descending colon to the rectum (Fig. 1). Proctosigmoidoscopy revealed pale mucosa with a bluish cast. During this period nasogastric suction and intravenous hyperalimentation were maintained and the patient continued to pass small amounts of liquid stool. On 9/17, 8 weeks following the transplant operation, a tender left lower quadrant mass was first noted. It increased in size over the next six days, and exploratory laporatomy revealed acute pancreatitis, a purulent exudate over the mesentery of the small bowel and colon, and necrosis of the descending and sigmoid colon, which were resected. Peritoneal fluid cultures grew *Escherichia coli* and *Pseudomonas aeruginosa*. Intravenous cephalothin and garramycin were started on 9/27. Because of continued fever and cyanosis of the colostomy, the patient was returned to the operating room, where resection of the distal transverse colon and proximal rectum were performed. The serum creatinine at this time was 2.5 mg% and prednisone and azathioprine doses were 60 mg and 37.5 mg respectively. On 10/1 gram negative anaerobic rods were cultured from the abdominal drains, and chloramphenicol was added to the antibiotic coverage. The patient had a respiratory arrest with aspiration on 10/3 and, although immediate resuscitation was accomplished, he remained unresponsive and was declared dead on 10/6. Pathologic specimens revealed acute pancreatitis, massive fat necrosis and acute inflammatory reaction in the mesentery, and thrombosis of the veins and arteries of the mesentery. The colonic mucosa was pale, edematous, with no discrete ulceration or hemorrhage, indicative of a potentially reversible ischemic change. It was concluded that acute pancreatitis with severe peritoneal inflammation could account for the pathologic findings in the mesentery. No episodes of hypotension or intestinal obstruction were noted during the post-transplant period and the ischemic colonic changes appeared to be related to hemoconcentration and subsequent occlusion of the colonic vasculature.

Case 2. J. A., a 21-year-old Negro male, engineering student received a cadaver renal allograft on 1/9/73. The anastomoses were performed in an end-to-end manner with the renal and right hypogastric arteries and end-to-side with the renal and right common iliac veins. The patient had a very stormy postoperative course including re-exploration for retroperitoneal hemorrhage on the first postoperative day and three courses of intravenous methylprednisolone (3 gms per course) during the first three months. In addition, the patient received 1350 rads to the allograft in right iliac fossa and was treated with carbenicillin and cephalothin for a wound infection with *Pseudomonas aeruginosa* and *Staphylococcus aureus*. At the time of discharge, 4/3/73, a serum creatinine was 2.3 mg% and prednisone and azathioprine doses were 27.5 mg and 75 mg respectively. The patient did well until 6/22/73 when he was readmitted with abdominal pain, diffuse abdominal tenderness, and fever. Exploratory laporatomy revealed perforation of the gall bladder, and a cholecystectomy was performed. Postoperatively a right lower lobe pneumonia developed. Sputum cultures yielded *Escherichia coli* and cephalothin therapy was again started. Immunosuppression included azathioprine 37.5 mg and prednisone 25 mg. Between 7/1 and 7/23/73, renal function deteriorated despite two more intravenous boluses of 1 gm methylprednisolone and hemodialysis was reinstituted on 7/12/73. A pseudomonas urinary tract infection was treated with intravenous carbenicillin and by mid-August, with the exception of intermittent low grade fever, the patient was ready for discharge. At that time he was receiving only oral oxacillin for a staphylococci infection of his arteriovenous shunt site.

The patient was discharged on 8/28/73, taking a number of antihypertensive agents and 25 gm of an ion exchange resin daily. Continued low grade fever as an outpatient eventuated in readmission for removal of the cadaver allograft on 10/31/73 and the patient became afebrile on no antibiotics or immunosuppressive agents.

On 1/9/74 the patient developed crampy abdominal pain, fever, diarrhea, nausea and vomiting, at first attributed to a viral gastroenteritis. An upper gastrointestinal series was normal; however, barium enema revealed edematous thickening of the left transverse colon. Continued low grade fever, intermittent abdominal pain on hemodialysis, and occasional diarrhea led to repeat barium enema revealing an irregular edematous descending colon, asymmetric haustration of the sigmoid colon and sacculation in the region of the splenic flexture (Fig. 2). Proctoscopic examination was normal.

A clear liquid diet and intermittent intravenous fluid support was required for approximately three weeks following the second barium enema, after which the patient became asymptomatic. He has returned to graduate school and is doing well on hemodialysis. Repeat barium enemas have been normal.

Other than the intermittent use of an ion exchange resin for control of serum potassium, no medications were being used at the time of the colonic ulceration. The specific etiology of the colonic lesion is unclear.

Case 3. D. I., a 34-year-old Negro man, received a cadaver renal allograft placed in the right iliac fossa on 6/6/74. (End-to-end: Renal to hypogastric artery, end-to-side: renal to iliac vein). The first rejection occurred during the fourth postoperative week, prior to which the patient had had no complications. Three grams of methylprednisolone, (one gram intravenously per day on three successive days) were administered during the fourth, fifth and seventh postoperative weeks, in addition to a second and third course of 450 rads directed at the kidney. During the week between the second and the third "pulses" of methylprednisolone, the hematocrit dropped from 19 to 12%, associated with the passage of several bright red to mahogany-colored stools. The leukocyte count at this time was 1200, platelet count 104,000 and the prothrombin time 17.0 seconds, compared to a control value of 12.0 seconds. The partial thromboplastin time was 69 seconds (N = 28– 35 sec). A barium enema revealed "irritability" in the distal descending colon. Stool culture was positive for Salmonella, type B. Three units of leukocyte poor, washed, packed erythocytes were administered, and ampicillin (2 grams, p.o., q.i.d.) was started. Sigmoidoscopic examination revealed a rosette of external hemorrhoids, however, no mucosal lesions were noted. Cytomegalovirus titer was 1:32.

Within one week of the rectal bleeding, the hematocrit returned to a stable level of 21%, coagulation parameters had become normal and stool cultures grew normal flora. A renal biopsy performed during the fifth post-transplant week revealed acute and chronic rejection, and the oral prednisone which had been tapered to 60 mg. daily was increased to 300 mg daily. Azathioprine dosages had been lowered because of the leukopenia. Continued renal functional deterioration necessitated return to hemodialysis during the ninth postoperative week, and allograft nephrectomy was required because of local tenderness and fever at three months. It was thought that a salmonella enteritis was superimposed upon a coagulation abnormality, producing a picture indistinguishable from transient ischemic colitis. There were no periods of hypotension other than that which occurred during the acute hemorrhage, and no evidence of intestinal obstruction was noted. Thepatient received a second cadaver renal allograft on 2/7/75. Because of the presence of a polar artery, the patient's left hypogastric artery and one of its branches were used for anastomosis to the renal vessels. Although the second kidney underwent acute rejection within three weeks and was removed no untoward effects on the colon secondary to ischemic changes were noted.

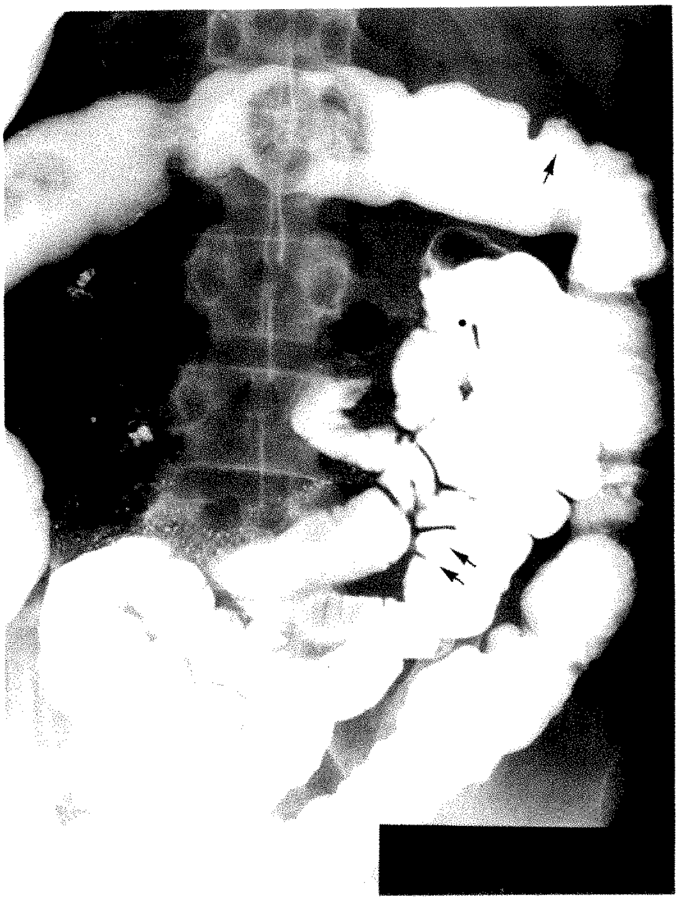

FIG. 2. Barium enema examination, Patient 2. Note edematous mucosa of the proximal descending colon, sacculation of the region of the splenic flexure (single arrow) and asymmetric haustration of the sigmoid colon (double arrows).

Case 4. C. J., a 22-year-old Negro woman, received her first cadaver renal allograft, placed in the right iliac fossa in February, 1972. Anastomoses were end-to-end: right hypogastric to renal artery and end-to-side: renal vein to external iliac vein. Early acute rejection necessitated return to dialysis and ultimately the kidney was removed. Transplantation of a second cadaver renal allograft was performed. Anastomoses were identical to the first kidney except for placement in the left iliac fossa. On 1/23/75, however, a biopsy of the kidney taken one hour after re-establishment of blood flow revealed many fibrin thrombi "consistent with hyperacute rejection or perfusion injury," despite a negative crossmatch preoperatively. Although 4000 ml of urine were produced in the first 12 hours, the patient suddenly became anuric, a technetium 99m DTPA flow scan revealed minimal flow, and the patient was returned to the operating room. Inspection of the kidney revealed essentially total infarction despite a strong pulse in the renal artery and its primary branches, and it was removed on the first postoperative day. Immunosuppression (which had consisted of 3 gms of intravenous methylprednisolone and 500 mg of azathioprine) was terminated. On the fourth day after allograft nephrectomy, the patient began to complain of left lower quadrant pain and the rectal temperature was 101.4°. Bacteriodes fragilis was cultured from the blood stream and ampicillin (6 gms/day) was started. Because of continued low-grade fever and abdominal pain, proctoscopy was performed, revealing pale mucosa. A barium enema showed areas of fine, saw-tooth irregularity and pseudopolypoid filling defects in the descending colon on 2/11 (Fig. 3). An upper gastrointestinal series with a small bowel follow-through was normal. Fever persisted on ampicillin, and chloramphenicol was substituted. Guaiac-positive diarrhea began on 2/20, and a repeat proctosigmoidoscopic examination revealed pale rectal mucosa and small discrete mucosal ulcer at 12 cm. A second barium enema showed an area of narrowing in the descending colon and "thumb printing" of the proximal descending colon consistent with ischemic colitis (Fig. 4a). Stool culture grew normal flora and a CMV titer was 1.4. The pain in the left lower quadrant worsened and began to radiate to the left upper quadrant in association with a temperature elevation to 102.8°. A third barium enema revealed numerous fine ulcerations in the descending and sigmoid colon and rectum. Because of increasing pain and continuous temeprature elevation, the patient underwent an exploratory laparotomy on 3/15/75. The colon was found to be severely ischemic with multiple areas of infarction from the splenic flexure to the rectum. A left colectomy was performed, leaving the patient with a left transverse colostomy and a sigmoid mucous fistula. Pathologic

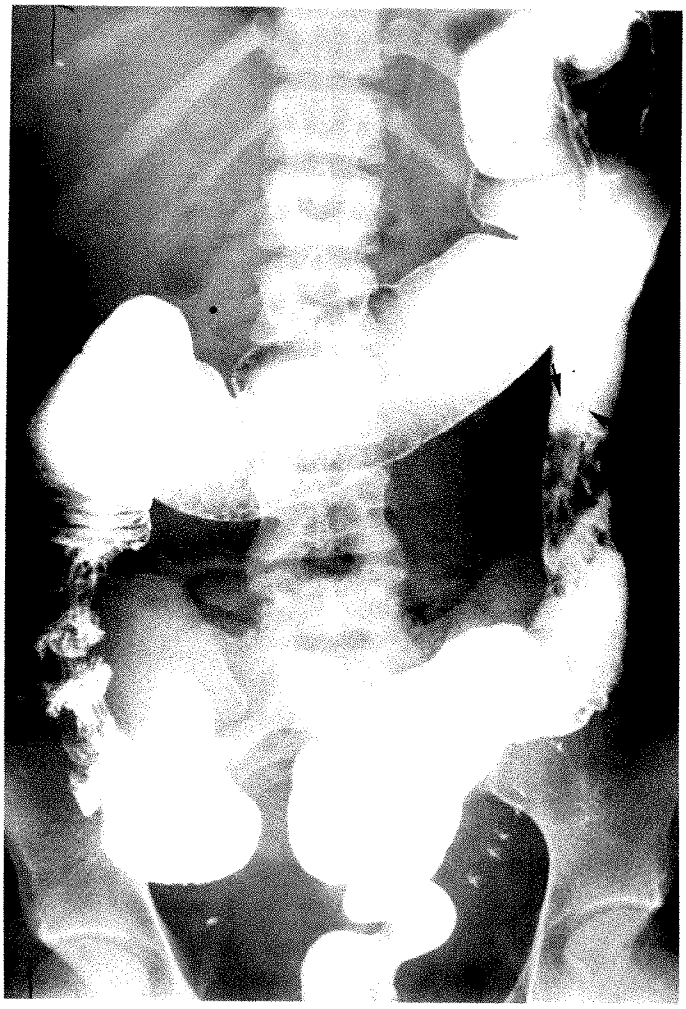

FIG. 3. Barium enema examination, Patient 4, 2-11-75. Note fine "saw-tooth" irregularity along the upper descending colon with pseudopolypoid filling defects in the lower descending colon (arrows).

diagnosis revealed a necrotic colon with an extensive mucosal loss and prominent edema of all layers. A diffuse, acute inflammatory infiltrate was noted, and the external muscle layers showed degenerative changes (Fig. 4b). In addition to the three barium enemas, the patient received ion exchange resin by rectum and by mouth during the two weeks following the allograft removal. The patient left the hospital four weeks following the colectomy and is presently awaiting colostomy closure and retransplantation.

Discussion

The etiologic mechanisms involved in the development of the colonic lesions in the four cases presented above are multifactorial and concomitant. They have been categorized clearly by Bernstein et al.[4] into five groups: 1) uremia; 2) blood volume redistribution; 3) immunosuppressive therapy and its complications; 4) antibiotic therapy and its complications; and 5) irradiation. To these may be added one more category: 6) retroperitoneal surgery with ligation of the collateral arterial supply to the colon. These mechanisms will be considered in reference to our patients.

1. Uremia

As noted by Bailey et al.,[2] the uremic patient is prone to many colonic complications including a 9% incidence of ulceration and perforation. Bleeding from small ulcers may occur anywhere in the gastrointestinal tract and bloody diarrhea is not uncommon, especially in patients undergoing chronic hemodialysis with systemic heparinization. The exact causes of the bleeding tendency of uremic patients is not known. Capillary fragility may be increased and platelet function and absolute number may be decreased, especially in those uremic patients with hypersplenism. Stewart et al.,[28] have noted, however, that some of the coagulation defects may be partially reversed by adequate dialysis. Three of four patients developed their colonic lesions at a time when renal functional deterioration was marked; two of the patients having already returned to hemodialysis. Case 1, H. H. had a serum creatinine of 1.5–2 mg% at the time of his exploratory laparotomy.

2. Blood volume redistribution and retroperitoneal surgery.

The recipient of a renal allograft, despite the usually young age, frequently has peripheral vascular changes which are indistinguishable from those seen in the nonuremic patient with generalized peripheral vascular disease. The accelerated atherosclerosis and hyperlipidemia, important potential risk factors in the etiology of cardiovascular disease in patients on chronic hemodialysis[8,20] may often result in occlusion or severe stenosis of the very vessels which are used for anastomosis to the renal artery of the allograft, i.e. the common iliac artery and its major branches, the external and internal iliac arteries. These vessels occasionally require endarterectomy before use, and their condition is likely to reflect that of the mesenteric circulation as well. The trauma of a retroperitoneal dissection added to the contracted intravascular volume of the transplant recipient may produce a situation in which less than optimal flow is carried by the pelvic and mesenteric vessels. This situation, if prolonged, can easily be seen to produce a low flow state in the major arterial and collateral supply to the colon *i.e.* the superior and inferior mesenteric, hemorrhoidal, and right, middle and left colic arteries, resulting in occlusive or non-occlusive ischemic damage to the colon. Further, a patient who has rejected a previous renal allograft and receives another placed in the contralateral iliac fossa, may be at increased risk in that the colonic arterial collaterals via the hypogastric arteries are destroyed bilaterally as in Patients 3 and 4. The importance of these collaterals is noted in a number of reports of colonic ischemia following infrarenal aortic surgery.[5,15,16,26]

In addition to the direct compromise of the mesenteric circulation, indirect embarrassment of the circulation

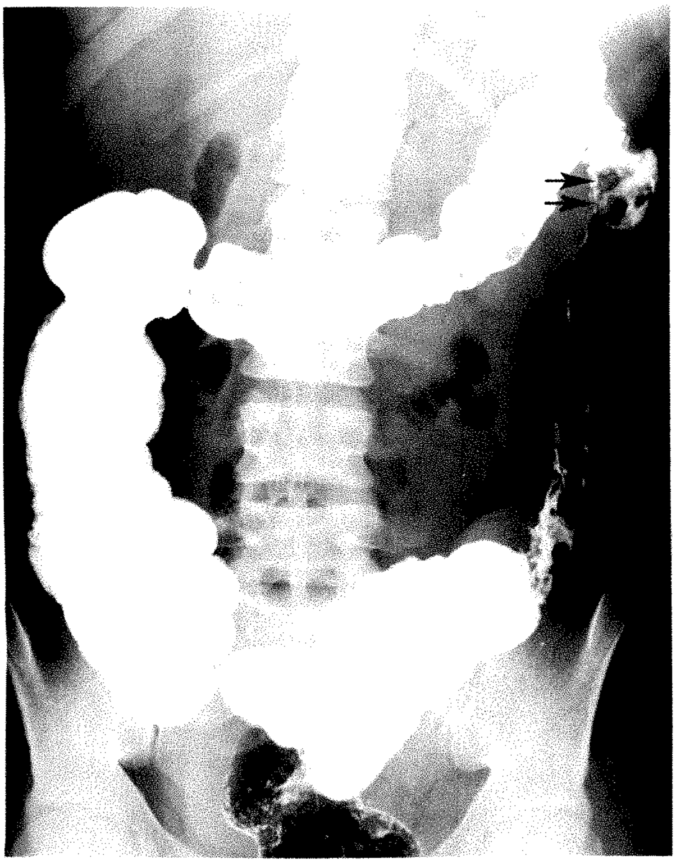

FIG. 4a. Barium enema examination, Patient 4, 20-20-75. Note persistent irregularity and slight narrowing of the descending colon. "Thumbprinting" (arrows) can be seen in the proximal descending colon.

to the colon may follow colonic distention of significant degree. This phenomenon is not uncommon in the uremic patient who has received multiple doses of an ion exchange resin, which alone or in combination with routine antacid therapy usually used in steroid-treated patients, may produce an "obturator" obstruction of the colon as the material becomes dehydrated and inspissated.[3] Furthermore many uremic patients have a form of autonomic insufficiency[18] which, if the gastrointestinal tract is involved, may allow for atony and distention of the colon. Finally, the combination of a massive diuresis in the immediate post-transplant period, the hemorrhagic tendency of the uremic patient, the stress of surgery on a myocardium possibly compromised by long standing hypertension, chronic congestive heart failure, or pericarditis calls for skillful manipulation of the fluid balance in the 24–48 hours following transplantation, attempting to avoid hypotension and hemoconcentration at all times.

3. *Immunosuppressive therapy*

Most organ transplantation centers use adrenocorticosteroids and azathioprine or cyclophosphamide, to which may be added other agents such as antilymphocyte serum (ALS), actinomycin D, antihistamines, and local irradiation to the allograft. Since their introduction, steroids have been associated with unusual gastrointestinal complications, including gastric, duodenal, and cecal perforation, acute pancreatitis, and peripancreatic fat necrosis. There is some controversy regarding the incidence of duodenal ulcer in steroid-treated patients compared to incidence in the general population, however there is the general clinical impression that these agents aggravate but do not initiate ulcer formation because of their generalized effect on the healing process. Tissue culture studies by Dougherty and White[10] have shown that corticosteroids inhibit cellular proliferation, decrease collagen deposition, and reduce polysaccharide deposition. The living fibroblast cells are immobile, appear swollen and demonstrate no pinocytosis.

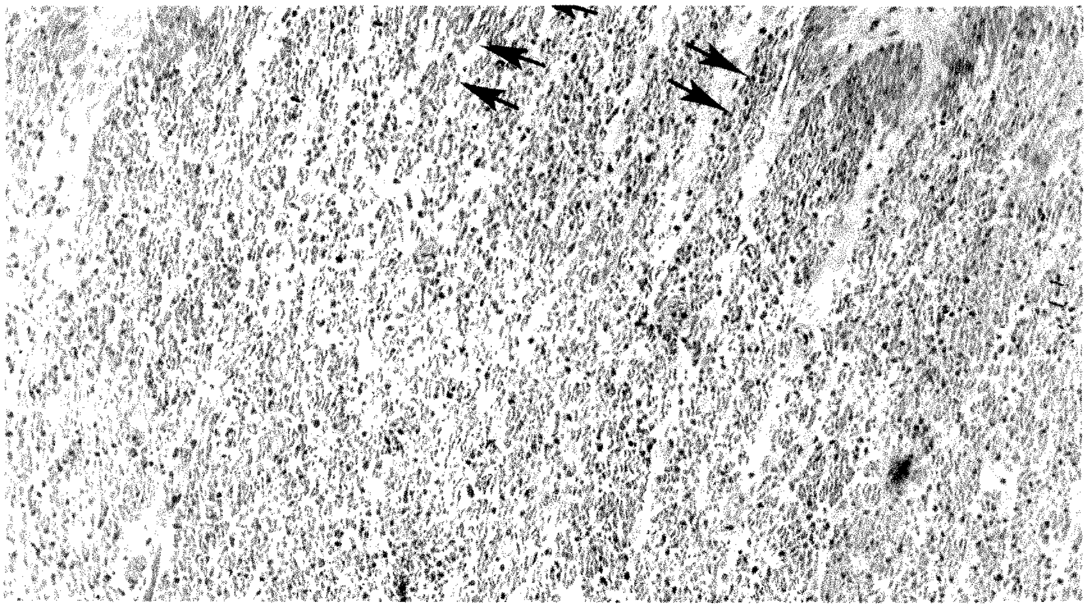

FIG. 4b. Photomicrograph of section of necrotic colon removed from Patient 4. The external muscle layers show marked degenerative changes (arrows) and there is a diffuse actue inflammatory reaction.

Indirect evidence for the deleterious effect of steroids on the gastrointestinal tract is the finding of a decreased incidence of colonic complications in patients on lower doses of steroids because of alternate day administration or the use of adjunctive immunosuppressive drugs such as ALS.[4] Experience in ulcerative colitis also does not suggest an increased evidence of colonic perforation as a result of prolonged steroid therapy. Thus Goldgraber et al.[12] found, in their own series of 400 patients, an incidence of perforation of the colon of 2.5% before the introduction of steroids and 0.8% in 240 steroid-treated patients. However, azathioprine, another major immunosuppressant, has been implicated, along with the corticosteroids, in the depletion of the lymphoid tissue of the intestine. This might result in a decreased mucosal cell turnover and subsequent slowing of the healing and regeneration which may be required following ulceration secondary to vascular compromise.

Another effect of steroid therapy which may be of etiologic significance in the development of colonic ischemia is the phenomenon of steroid induced pancreatitis, which occurs in about 2% of transplant recipients,[19] and may result in dehydration, hemoconcentration, mesenteric fat necrosis and a decrease in mesenteric and colonic blood flow as seen in Patient 1.

Finally, because of the immunosuppressed state of the transplant recipient, a number of opportunistic pathogens may be allowed to flourish. One specifically implicated in colonic ulceration is the cytomegalovirus. Viruses have been associated with ulcers from the mouth to the rectum and have even been implicated as a causative factor in ulcerative colitis especially when intranuclear inclusion bodies are seen within the ulcer craters.[14]

Thus, the non-specific effects of immunosuppression are sufficiently damaging as to provide fertile ground for the destructive influence of ischemia and infection, resulting in the production of colonic ulceration.

4. *Antibiotic therapy*

Although discussed in this report as a separate category, the frequent use of antibiotics in renal allograft recipients follows directly from those conditions which predispose to frequent infections in these patients, i.e. uremia and immunosuppression. A wide spectrum of antimicrobial agents is in use in all transplant centers, and there are many reports of the lethal effects of the overgrowth of pathogens related to the supression of normal gastrointestinal flora. Pseudomembranous enterocolitis is an entity whose pathophysiology may be indistinguishable from that of ischemic colitis and the two have been discussed interchangeably in some cases.[17] Histologic changes seen in postoperative pseudomembranous enterocolitis include epithelial necrosis with erosion of the tips of the intestinal villi, necrosis of glandular epithelium, and congestion or occlusion of small venules and capillaries in the mucosa. The submucosa is found to be edematous and there is a network of fibrin and acute and chronic inflammatory cells in both the mucosa and submucosa.[6] Although staphylococci were originally considered to be the primary pathogen in the development of postoperative pseudomembranous enterocolitis, there are also reports of systemic fungal infections, particularly candida sepsis, related to enterocolitis.[17]

Antibiotic agents which have been directly implicated in hemorrhagic ulceration of the colon, and which may produce radiologic and pathologic changes identical to those seen in "classical" ischemic colitis are clindamycin,[27] lincomycin,[22] tetracycline,[25] chloramphenicol,[25] and ampicillin.[17] All of the patients in our report were exposed to at least one of these drugs before the development of the colonic lesions, and, in fact the symptoms of diarrhea and colitis have been observed up to several weeks following cessation of therapy with clindamycin. In addition, antiperistaltic agents such as diphenoxylate and opiates may aggravate or prolong the condition.

5. *Irradiation*

Another immunosuppressive modality is local irradiation to the allograft, which is thought to destroy those sensitized cells trapped within the graft and responsible for active rejection. Because of the high susceptibility of lymphoid cells to the effects of irradiation, relatively low doses may be given to the allograft without fear of irradiation damage to the gastrointestinal tract or kidney itself. The total dose of irradiation should be kept under 1350 rads. Although total body irradiation of doses greater than 900 rads will produce denudation of the gastrointestinal tract with hemorrhage and death in one to two weeks, in order to produce significant changes in the colonic mucosa by local irradiation, doses of 4500–5000 rads are required.[9] The lowest dose which has been associated with gastrointestinal injury is 2250 rads noted in a review by Gillies and Skyring,[11] Three of our four patients received three courses of 450 rads each during the post transplant period and the fourth received 150 rads once. There is little likelihood of irradiation induced colitis in these patients, although the threshold for injury may be reduced in the presence of other complicating factors such as renal failure, ischemia, or infections.

Review of Literature

In five large series of patients totalling 1156 allografts (3 hepatic)[1,4,13,23,24] 106 gastrointestinal complications occurred, an incidence of 9%. Eleven (10.4%) of these complications were considered to be colitis, colonic ulceration, or pseudomembranous enterocolitis. Duodenal ulcer, perforated diverticulitis, and hepatitis comprised the majority of the remaining complications. The age range was 8–60 years, but 8 patients were under 50 and 5 were under 40 years old. Five of the patients had rejections severe enough to require hemodialysis before the development of the colonic ulceration and at least 4 of the 11 patients were recipients of cadaver kidneys. Two additional patients required reoperation for repair of anastomotic urinary tract leaks.

The time of onset of the colitis ranged from one month to 18 months and the mortality rate for the 11 patients was 90%. Treatment included only fluid and blood replacement in 10 of the 11 patients including the one survivor. Two patients underwent infusions of pitressin into the superior mesenteric artery without success. One patient underwent exploratory laparatomy and died shortly thereafter of septic complications of the surgery.

Although there was no obvious relationship to immunosuppressive medication dosage, all of the patients reported in the literature were noted to have deteriorating renal function and probably high dose immunosuppression at the time of development of their colon abnormality. Although three of our 4 patients survived, one following colectomy, none has a functioning kidney at the time of this report.

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Estrogen Receptor and Natural Course of Breast Cancer

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The tumors from approximately 50% of patients with breast cancer contained estrogen receptor (ER). ER appeared more often and at higher levels in the tumors of postmenopausal women. Eleven out of 12 patients who had multiple ER assays from various metastatic sites showed no significant discrepancies in ER values. ER level appears to decrease as the duration of metastatic cancer increase. Patients with ER in the tumor more frequently have bone metastases than those without ER. Visceral metastases occurred more often with ER negative patients and appeared to have a more malignant course with significant shorter survival.

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BIOCHEMICAL MECHANISMS of hormone-target organ interaction have been recognized in the past several years. Polypeptide hormones and epinephrine react with target tissue by activation of membrane-bound adenyl cyclase which result in formation of cyclic AMP.[7] On the other hand steroid hormones appear to enter the target cells and bind to a specific extranuclear receptor.[4] Among the various steroid hormones, estrogen was given the most attention since it has been shown for several years to be related to animal and human breast cancer. Jensen and DeSombre[3] characterized estrogen receptor (ER) as a protein with the sedimentation coefficient of 8S which probably appears in the cytoplasm of target cell as 4S subunit. This estrogen receptor interacts with estradiol in the cytoplasm and undergoes transformation which is a temperature-dependent process. This transformed receptor-estrogen complex, which has a sedimentation coefficient of 5S, migrates to the nucleus and binds to the chromosome in the nucleus resulting in newly transcribed RNAs from the nucleus of target tissues. Whether this extranuclear receptor is merely a means of transporting the hormone into the nucleus or receptor protein itself is the active agent and hormone is only the activator for this receptor is not known at the present time.

Breast cancer tissue, both primary and metastatic, has been shown by several investigators[6] to contain ER. Some clinical aspects of human breast cancer associated with the presence or absence of ER in their tumor have been reported.[6] We are reporting here additional information regarding the natural course of breast cancer and ER in the tumor.

Materials and Methods

Breast cancer specimens both from primary sites and metastatic sites were obtained at surgery and frozen immediately; malignancy was verified by histological examination. All specimens were kept initially at −20 C, then transported to our laboratory in dry ice and stored at −70 C for longer periods.

The tissues were processed and assayed for estrogen receptor by gel-filtration technique as previously described.[2] One hundred milligrams of tissue were homogenized by a Willems Polytron in 10 mM Tris buffer, pH 7.4, containing 1.5 mM $MgCl_2$, 10 mM KCl, and 5 mM reducing agent, dithiothreitol. After spinning in a Spinco model L ultracentrifuge at 15,000 g for 15 minutes, the resulting supernatant fluid was spun at 100,000 g for 65 minutes, 4 C, using a SW 50.1 rotor and buckets equipped with adaptors (Beckman 305527). The supernatant fraction was diluted 1:1 with 10 mM Tris buffer, pH 8.5, containing 10 mM KCl, 5 mM dithiothreitol and 1 mM EDTA (column buffer) and Dextran Blue added. Protein was determined by the Folin method.[5] Immediately following centrifugation, 0.4 ml of

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the diluted supernatant fraction was incubated with 10 μl of (2,4,6,7-^{3}H)-estradiol-17β (100 Ci/mmole) standard for 2 hours at 4 C. A duplicate sample was also incubated with tritiated standard plus 100-fold excess of unlabeled estradiol-17β. Upon completion of incubation, each sample was chromatographed through a separate column containing 3–4 g Sephadex G-25 previously equilibrated in "column buffer." Flow rates were kept constant, and the void volume (5 ml, indicated by the Dextran Blue) was collected and extracted 3 times with ethyl acetate. An aliquot of the extract was counted in a scintillation spectrometer equipped with automatic external standardization.

Routine saturation curves were constructed for incubations with tritiated estradiol-17β and with labeled estrogen plus excess unlabeled estradiol-17β. Receptor levels were determined from the difference between total binding capacity at saturation of tritiated estradiol-17β and non-specific binding (residual binding in the presence of unlabeled estrogen). Occasionally Scatchard plots were used to calculate the binding constants of the estrogen receptor.[2] The level of 2.1 femtomoles (fmoles, 10^{-15} moles) estradiol bound per mg cytoplasmic protein or over was considered to be positive for estrogen receptor. This level or higher has been shown by us to correlate well with endocrine therapy response in disseminated breast cancer.[6]

Medical records of patients with diagnosis of breast cancer who had ER study on their tumor were reviewed. Patients with simultaneous bilateral breast cancer and patients with other active malignancy in addition to breast cancer were excluded. A total of 133 cases were found to be evaluable based on the above criteria. Most of the patients had an ER assay done only once; in 12 patients multiple ER assays were performed. In three of these 12 patients, the re-biopsy for ER test was carried out to study the effect of exogenous estrogen on the ER values.

Specific information regarding date of onset of symptoms, menstrual status at the time of ER assay, and the date and cause of death were determined. The sites of metastasis were divided into three categories as follows: viscera (includes liver, lung, pleura, CNS, spinal cord, and all intra-abdominal and intrathoracic organs), bone, and soft tissues (skin, opposite breast, lymph nodes). The term dominant site of metastasis is used to denote the category which is most extensively involved by cancer. In case of equal degree of multiple system involvement, the following priority of assignment was used: visceral, bone, soft tissue. The disease free interval (DFI) is defined as the time interval between initial diagnosis of breast cancer and the clinical diagnosis of disseminated cancer. The duration of disease was measured from the onset of cancer to the time of death.

TABLE 1. *ER Value in Pre and Postmenopausal Patients*

	Premenopause	Postmenopause
Total number of patients	31	102
Positive ER patients	14	54
Percentage of positive ER	45.2	53
Mean ER value (femtomole)*	23.4	39.7
Median ER value	7.0	12.9
Patients with multiple assay	0	12

* P = 0.40 by Student's t-test.

Results

Of 133 patients, 102 were postmenopausal women and 31 were premenopausal at the time the assay for ER was done. Sixty-eight patients or 51% had tumor which contained ER. As shown in Table 1, 53% of postmenopausal and only 45% of premenopausal patients had tumors which were positive for ER. The level of ER also appeared to be higher in postmenopausal cases.

The majority of patients under this study had metastatic breast cancer at the time ER assay was performed. Only 26 patients had ER study from primary breast cancer lesions while the disease was considered to be curable. However, 10 of them subsequently had recurrent carcinoma. Most of the patients had more than one organ involvement but the biopsy for ER study in general was carried out from the accessible lesions, i.e. skin, lymph nodes, breast masses. Biopsies from bones were possible when lesions were superficial such as from iliac crest area or more commonly when orthopedists operated on patients for various fractures. In many cases multiple visceral biopsies were obtained during surgery either for therapeutic purposes such as bilateral adrenalectomy or for complications arising from cancer such as intestinal obstruction. Table 2 indicates the sites from where the biopsy for each patient was obtained. It is not necessarily the only site of carcinoma involvement nor the dominant site of metastasis that the particular patient had. For example when a patient had recurrent breast cancer of the chest wall, bone, and with massive liver involvement, the biopsy for ER study was usually taken from the chest wall. The site of biopsy will be listed under soft tissue but the dominant site of metastasis will be classified as viscera.

Twelve patients had multiple biopsies. All except one had no significant discrepancy in ER value from various

TABLE 2. *Results of ER Values from Various Sites*

Sites of Biopsy*	Positive	Negative
Primary breast lesions	21	27
Soft tissue	40	35
Bone	6	1
Viscera	2	3

* See text.

TABLE 3. *Disease Free Interval*

	Positive ER 68 pts	Negative ER 65 pts
Free of disease	8	9
Inoperable cases	10	16
Mean DFI*	37.6	31.2 months
Median DFI	27.5	21.5 months

* P = 0.4 by Student's t-test.

sites of metastatic lesions, i.e. when the lesion from the skin was positive for ER, the lesions from lymph node and bone also were positive although the ER value from various sites may not be exactly the same. The one patient with a discordant ER value had ER of 31.6 fmoles from her primary breast lesion. Fifty-four months later the ER value obtained from a bone lesion was 3.5 fmoles but a negative ER value was found in a metastatic hepatic nodule. In Table 2 she was counted three times for the site of biopsy: primary, bone, viscera. The rest of the patients were counted once based on the first site of biopsy.

Disease Free Interval

Seventeen patients are still free of recurrent cancer. Twenty-six patients presented with inoperable breast cancer; 16 were ER negative patients. Therefore, in a total of 43 patients the DFI cannot be determined. In the remaining 90 patients DFI could be calculated but no significant difference was observed between the positive and negative ER groups as illustrated in Table 3.

Dominant Site of Metastasis

A total of 116 patients had recurrent or inoperable breast cancer. Fig. 1 shows a preponderance for bone metastasis in the positive ER group while in the negative ER group visceral metastasis appears dominant. The difference is highly significant with the P-value of 0.0001.

Patients with Multiple ER Assay

Of 12 patients with multiple biopsies, 11 had concordant ER value regardless of the site of the biopsy. Three were negative for ER and 8 were ER positive. There were 6 patients who were ER positive subsequently rebiopsied after a period of 6 to 54 months. All were found to have decreasing values of ER except for one who displayed an increase in ER 11 months after bilateral adrenalectomy as shown in Table 5. None of these 6 patients received estrogen or androgen during the 6 months preceding the second biopsy.

There were three patients who had ER assay performed while on Diethylstilbestrol (DES) 15 mg/day. One patient had ER assay prior, during and 4 months after DES therapy. The ER values were 3.3, 0 and 11.5 fmoles/mg protein respectively. The other two patients each had ER assays while on DES and repeat assay after DES treatment was discontinued. One patient's ER level rose from 0 to 2.2 and the other went from 4.8 to 61 fmoles/mg protein after discontinuation of DES for 4 and 7 months respectively.

Survival Data

Forty-eight patients had expired as of December 15, 1974; 21 were positive for ER and 27 were negative. Table 4 demonstrates the total duration of disease from onset of cancer to death in each category. All but two died of metastatic breast cancer; both had ER in their tumor. One died of toxicity from chemotherapy and the other died from pulmonary embolism 2 weeks after androgen therapy was initiated. Nine patients with negative ER had rapidly progressive disease which compelled the managing physicians to bypass endocrine treatment and initiate chemotherapy as the first systemic treatment for disseminated cancer. The difference in survival between ER positive and ER negative patients is statistically significant in favor of the ER positive group.

Comment

Lower ER level in the premenopausal group is probably due to partial saturation of the receptor sites by endog-

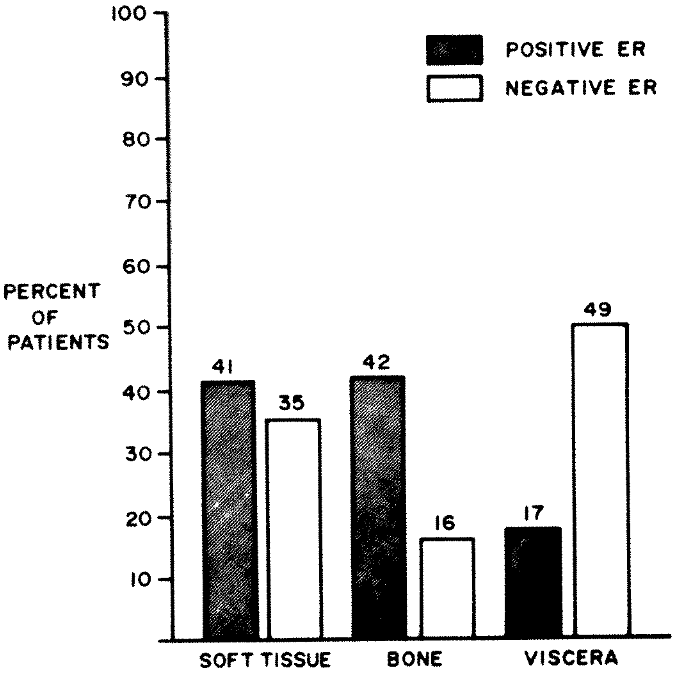

FIG. 1. Comparison of dominant site of metastasis between ER positive and ER negative group. More bone metastasis occurs in ER positive and more visceral metastasis in ER negative groups. Fisher test for P = 0.001 for bone vs viscera and P = 0.01 for soft tissue vs viscera.

enous estrogen. The study of ER values in three patients while on and off therapy with DES seemed to be in agreement with this hypothesis, although the dose of DES used was much higher than the physiological amount of estrogens present in normal premenopausal women. It has been suggested that the critical level of ER in postmenopausal women to be considered as positive should be higher than premenopausal patients. On the other hand, several investigators[6] reported good correlation of response to endocrine therapy in patients with borderline ER value. The interpretation of an ER value in a patient with disseminated cancer who is receiving or recently received estrogen therapy must be interpreted with caution because of the possibility of a false negative ER value. The binding between estrogen and receptor protein is strong. This tight binding appears to result from a slow rate of dissociation.[8] How much time is required for the receptor sites to be freed up again after discontinuation of estrogen treatment is not known. The three patients who had re-biopsies for ER assays after interruption of DES for periods of 4 to 7 months showed increased ER levels. It is quite conceivable that less than 4 months is required for the receptor sites to become unsaturated. The fact that 11 out of 12 patients who had multiple ER determinations which were concordant would suggest that in most cases single biopsy of an accessible lesion is adequate for ER study. However when a change in endocrine therapy is contemplated, a repeat biopsy of an accessible lesion, when available, should be performed. This is to insure the presence of hormonal dependent cells in the tumor prior to institution of a new form of endocrine therapy. This is particularly important when major surgery such as bilateral adrenalectomy or hypophysectomy are involved. The fact that 5 of 6 patients in this study showed a progressive decrease in ER value as the duration of metastatic disease increased, as shown in Table 5, appears to support the hypothesis that a patient whose tumor contains ER actually has both hormonal dependent cells and independent cells but in different proportions. After receiving endocrine manipulation, the hormonal dependent cells are destroyed allowing the hormonal independent cells to proliferate. The alternative explanation is the continuous existence of hormonal dependent cells, but ability to produce ER is lost after endocrine treatment. On the other hand, a patient with no ER in the tumor probably has few or none of hormonal dependent cells in their tumors.

The clinical course of disseminated breast cancer, in general, correlates with the sites of metastasis and DFI. Patients with a long DFI or metastatic involvement of skin, lymph nodes, or bone without visceral metastasis are found to have a longer survival compared to those with visceral metastasis.[1] Our ER study seems to coincide with the above clinical observations, with the exception of the prognostic role of DFI for which there was no difference between positive and negative ER groups. Patients with ER negative tumors more frequently have visceral involvement, whereas those with ER positive have predilection for bone involvement. The survival was significantly shorter in the ER negative group. Because the inoperable breast cancer in the ER negative group outnumbered those in the ER positive at a ratio of 8 to 3, one may raise the question that the poorer prognosis in the ER negative group could have been the result of excessive patient procrastination in seeking medical treatment. However, in review of the medical records in those 11 cases who presented with inoperable breast carcinoma, the median delay in getting medical attention was 5 months (range 1–12) in the ER negative group as contrasted with 12 months (range 1–13) in the positive ER group. Moreover, 5 out of 8 patients in the negative ER group, at the time of initial diagnosis, had visceral metastases in addition to breast lesions. However, only one out of 3 in the positive ER group had visceral involvement at the time of diagnosis of breast cancer. These findings tend to support the hypothesis that the biological behavior rather than procrastination by the patients is the reason for shorter survival in ER negative patients.

TABLE 4. *Duration of Disease*

	Positive ER 21 cases	Negative ER 27 cases
Mean*	56.7	29.6 months
Median	54	23 months
Chemotherapy only	1	9
Endocrine therapy only	5	3
Endocrine and chemotherapy	15	15
Inoperable case at initial diagnosis	3	8

* $P < 0.01$ by Student's t-test.

We feel that ER study should be done in every patient with breast cancer regardless of operability. A significant number of patients who undergo potentially curative mastectomy will eventually have recurrent cancer. If cancer recurs in bones or viscera, frequently the biopsy for ER assay cannot be done either because of technical

TABLE 5. *ER Level in Patients with Multiple Sequential Assay*

Name	1st and 2nd ER level fmoles		Treatment between 2 ER	Duration between 2 ER (in mos.)	Sites of biopsy
E.F.	31.6	3.5	Adr., chemo.*	54 M	Primary, bone
W.B.	80.4	8.3	Adr.	7 M	Skin, skin
V.T.	32	0.9	Adr.	6 M	Skin, skin
H.B.	41.3	5.4	Adr.	8 M	L.N., L.N.†
G.G.	14.6	6.5	Adr.	7 M	L.N., L.N.
G.T.	14.2	80.7	Adr.	11 M	L.N., L.N.

* Adr. = bilateral surgical adrenalectomy.
† L.N. = lymph node.

or ethical reasons. The only tissue available for ER assay in these individuals would be the primary lesions. It is proposed that ER study not only can guide the physician in selecting the appropriate type of therapy for disseminated cancer but in our opinion it can provide additional information regarding prognosis and probable future sites of metastasis.

Addendum

Since the submission of this article, 8 more patients whose tumors contained ER were subjected to repeat biopsies for ER after termination of endocrine therapy (and in some cases after both endocrine and chemotherapy). All 8 patients showed decrease in ER value in the second ER assays. Not all patients responded to endocrine therapy.

Acknowledgment

The authors wish to thank Mrs. Cynthia Van De Walle for her statistical assistance in this study.

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Letters to the Editor

April 15, 1975

Dear Editor:

Moreno and his associates have recently presented evidence suggesting that spontaneous reversal of portal blood flow in cirrhosis is a rare occurrence if it happens at all. This conclusion was reached in the article entitled "Spontaneous Reversal of Portal Blood Flow: The Case for and Against its Occurrence in Patients with Cirrhosis of the Liver", Annals of Surgery 181:346, 1975. In the text of that article, they refer to some of our previously published work and raise one or two questions which deserve an answer. In one instance they note that we have mentioned a patient with spontaneous reversal of portal flow as detected by the electromagnetic flowmeter, but indicate that we did not record the magnitude of that flow.[1] It is indeed correct that the volume of flow reversal was not stated since the patient was merely cited as an example of a patient with reversed portal blood flow which was not demonstrated by wedged hepatic venography. The volume of reversal of flow, however, was measured at 100 ml/minute.

The authors also suggest that this patient is omitted from a later report concerning the validity of preoperative hemodynamic studies.[2] In fact, the patient is included in the data in that report. Since the thrust of that article was to define hemodynamic stages on the basis of maximum perfusion pressure, no specific flow data were presented. However, in the section on "Results", the HA:PV flow ratio was statistically correlated with maximum perfusion pressure and used to define hemodynamic stages on this basis. In Table 2, this patient was one of the three patients classified as Stage III, and was the only patient in the entire group with a negative maximum pressure.

We have measured portal blood flow with the electromagnetic flowmeter in only 18 patients, and in one of these patients spontaneous flow reversal was demonstrated as indicated. In this case, the maximum perfusion pressure was, as predicted, negative. We have seen an additional 6 patients with a negative maximum perfusion pressure, but unfortunately portal blood flow measurments were not made. This one patient, however, does document that spontaneous reversal of portal blood flow can occur in the cirrhotic patient with portal hypertension and that such reversal can be associated with a negative maximum perfusion pressure.

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2. Smith, G.W.: An Assessment of the Validity of Preoperative Hemodynamic Studies in Portal Hypertension. Surg., 74:130, 1973.

April 29, 1975

Dear Editor:

My associates and I are pleased to learn that Smith did measure the magnitude of the reversed portal flow in his patient. In his present letter he offers such magnitude for the first time and, in so doing, he goes on the record as having measured the only instance of spontaneous reversal of portal flow in cirrhosis among 273 measurements reported in the world literature. As we said in our article, this single patient constitutes the strongest support for the hypothesis of spontaneous reversal of flow and, at the same time, gives a clear example of the extreme rarity of this phenomenon. Actually, the thrust of our paper was to emphasize the futility of elaborating on a subject which, at best, is so uncommon as to have only marginal clinical significance.

With respect to the inclusion or omission of this patient in his later report, we had to assume that the patient was omitted. The reason for our assumption is the simple fact that a reversed portal flow would result in a negative HA:PV ratio and nowhere in the report one can find any reference to negative ratios.

Although our paper did not deal with any attempt to correlate the HA:PV ratio of flows with the so called "maximum perfusion pressure," Smith's reference to it in his letter opens the door for some discussion of the subject. In the first place, it is frought with dangers to perform a regression analysis on the basis of the mean values of any variable grouped according to arbitrary cut-off limits. Then, it is difficult to conceive any physiological or pathological reason that would justify a correlation between the ratio HA:PV and the "maximum perfusion pressure." We have measured this ratio in 41 patients with cirrhosis and portal hypertension[1] and found a wide spread of its value ranging from 0.23 to 4.71 with a mean value of 1.13 ± 1.01 S.D. What is more important, in 22 of these patients we had also the value of the "maximum perfusion pressure" and we found a complete lack of correlation ($r = -0.12$) between this pressure and the ratio HA:PV (see Fig. 10 in our reference 1). Not having the raw data in the studies by Smith we can only speculate that his correlations may have been biased by the bracketing of his patients in small groups. He gives a plausible example of this possible bias in his letter while stating that in Stage III he had values of HA:PV in only three patients. If one subtracts one degree of freedom used in the determination of the mean, the value of the latter and of its standard deviation becomes highly questionable. The problem is aggravated by the fact that one of these three patients, the one with reversed flow, must have had a negative HA:PV ratio.

Finally, the association of a negative "maximum perfusion pressure" with his case of reversed portal flow should not imply a cause-effect relationship. In a previous paper[2] we have shown that the splanchnic and hepatic occluded portal pressures used in the construction of the "maximum perfusion pressure" are unrelated to the magnitude and direction of the portal flow. With the portal vein occluded by a clamp, the hepatic and splanchnic occluded portal pressures are determined uniquely by the ratio of the outflow to the total resistance in the hepatic artery-hepatic vein and in the splachnic-collateral parallel circuits.

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June 27, 1975

Dear Editor:

The article entitled "A Review of Echinococcal Disease," by Lewis, Koss, and Kerstein in the April, 1975 Annals makes many excellent points concerning a disease which can pose extremely complicated problems in treatment.

The French literature presents an enormous experience with Echinococcosis and some points of view there concerning hepatic forms of the disease merit emphasis.

Most surgeons protect the abdominal contents with pads saturated with two percent formalin. A distinction must be made between simple and complicated cysts. The simple, young cyst containing clear fluid can be treated by simple removal of the hydatid membrane; it is rarely necessary to treat the remaining soft-walled cavity further.[2] The older, multivesicular parasite has a thick, often partially calcified second wall of compressed hepatic tissue. These are the cysts frequently complicated by openings into the bile ducts. Their treatment of choice is cystectomy, which may entail anatomic hepatectomy.[1] Arteriography and cavography are best used to assess the vascular risk of this sometimes hazardous undertaking. If cystectomy is impossible or judged too dangerous, partial resection with drainage is accomplished.[4] Biliary orifices are sought and sutured. In complicated cysts we feel T-tube drainage of the main bile duct is mandatory since bile leakage and/or infection are otherwise almost inevitable.[3]

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Dear Editor:

Dr. Corlette had recently written to us, and it is clear that he indeed has had an extensive experience with this problem while working in France. We do not recommend the use of Formalin even on pads protecting the abdominal contents because although some authors feel that one-half to one per cent Formalin is safe, most are agreed on the fact that greater concentrations are probably unsafe and that even on pads which are protecting the abdominal contents, enough can be absorbed which may cause harm. We have used 20 per cent hypertonic saline and feel that this is a safer technique and affords adequate protection during the opening of the cyst. In the simple young cyst containing clear fluid as described by Dr. Corlette, the technique of capitonnage or some other technique such as filling the cavity with omentum would seem to be one added step which should result in more rapid healing of the liver and better recovery. On the more complicated cyst, which, as Dr. Corlette states may require cystectomy and possible partial hepatectomy, we feel that both our use of the term "hepatic lobectomy" as well as Dr. Corlette's statement "anatomic hepatectomy" should probably be replaced by the term *appropriate hepatic resection,* as it has been shown by Lin (Lin, T.: Simplified Techniques for Hepatic Resection, Ann. Surg. 180:285-290, 1974) that neither lobectomy nor anatomic hepatectomy is necessary, but with appropriate surgical techniques, just the area of involvement may be removed.

As stated in our article, arteriography is an excellent adjunctive technique for determining the amount of involvement of liver parenchyma. When and if echography (ultrasound) techniques are perfected, they also may be of benefit as another non-invasive procedure. We are in complete agreement with the use of T-tube drainage in complicated cysts and those eroding with the cannaliculi and main ducts, as stated at the conclusion of our article.

In summary then, aside from our disagreement with Dr. Corlette on the use of Formalin, we are in basic agreement in each of the four other points which he brings up, and we so stated in the article. The points are certainly important and deserve such emphasis.

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September 15, 1975

Dear Editor:

In assessing the outlook for small bowel malignancies, two large series were reviewed in the August issue of Annals of Surgery. In both reports, the authors attribute the high mortality rates to a failure to seek medical attention until long after the onset of symptoms. Our recent experience with patients in a different economic setting casts doubt upon the validity of this explanation.

From 1970 to 1974, 10 patients with primary small bowel malignancies were treated at the US Naval Hospital, Bethesda, Maryland. Since these patients had easy access to medical care without regard for cost or loss of income, one might have expected that they would avail themselves of this care soon after noticing any symptoms. This was indeed the case, but the expected benefit of earlier diagnosis was not obtained.

In contrast with the 12 to 18 months' delay reported in the other two series, our patients sought treatment within a maximum of 6 months after onset of symptoms. The composition of this group was similar to the two larger series, with an age range of 14 to 74 years (mean 40) and a 4 to 1 ratio of males to females. Their presenting symptoms were likewise abdominal pain, anemia, weight loss and abdominal mass. The microscopic diagnoses were also similar to the larger series, with no preponderance of rare or "good outlook" tumors.

Unfortunately, our results were also similar to theirs. Only three of the original 10 patients are alive 2 to 4 years after diagnosis.

Earlier diagnosis must certainly offer the only currently plausible hope for better results in these diseases. However, mildness and lack of specificity of the early symptoms make it very unlikely that patients will ever seek help early enough after onset, even in the absence of financial worries, to be able to improve their outlook to any significant degree. The paucity of early physical signs also makes it unlikely that routine physical examination will be very helpful.

It seems more likely that the hope for substantially improved treatment for small bowel malignancies lies in the development of new diagnostic methods. Such approaches would include techniques for examining the systemic biochemical, endocrine and immunologic responses to a hidden tumor. The rarity of these particular tumors, along with the absence of any identifiably high risk group, dictates that any test must be feasibly applicable on a broad, screening scale at reasonable cost and convenience. Until the means are found for prevention, a vigorous investigation of symptoms and the prompt clinical application of any new approaches developed in the research laboratories will continue to offer the only possibility for relief from malignancies which grow silently in inaccessible places.

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The opinions or assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

September 19, 1975

Dear Editor:

Thank you for the opportunity of reading the comments of Drs. Oller, Rice and Herman.

I am in general agreement with their statements regarding small bowel malignant tumors. I have read our own paper carefully once more and am unable to find a statement to the effect that patient delay was considered a cause for delay in diagnosis or treatment.

The delay in our series between the onset of symptoms and surgery (adenocarcinoma 6 months, leiomyosarcoma 8 months and carcinoid 12 months) was unquestionably more on indication of difficulty in diagnosis, than attributable to delay in seeking medical advice. Only 35% of our patients were correctly diagnosed preoperatively.

We emphasize the lack of specificity in the symptoms of small bowel tumors and state that small bowel tumors should be suspected whenever signs of obstruction or bleeding remains unexplained after conventional workup.

I would be interested in knowing how the surgeons at Bethesda were able to decide on an early operation in the absence of positive diagnostic findings, realising that the difference reported may relate to the small number of patients.

The New York Hospital—
Cornell Medical Center
New York, New York

Dear Editor:

We are in general agreement with the views expressed by Drs. Oller, Rice, and Herman.

Based on the concept that a tumor arises from a single cell, the majority of neoplastic growth occurs before the development of clinical cancer.[1] Consequently, reliable laboratory detection of small bowel lesions in the preclinical phase based on biological alterations in these abnormal cells certainly is a major goal for the future.

Nevertheless, we know that clinical staging of disease correlates with prognosis for all bypes of neoplasms.[1] Therefore, we believe that clinicians have the opportunity to improve prognosis by vigorous investigation of admittedly vague but suggestive symptoms.

It should also be pointed out that the prolonged interval between onset of symptoms and treatment relates to both *patient delay* in seeking medical assistance as well as *physician delay* in making the diagnosis and undertaking appropriate treatment. The figure of six months' delay referred to in Dr. Oller's series relates only to the former category of delay whereas our discussion considers the duration of symptoms from their onset to their diagnosis.

Our view continues to be that earlier clinical diagnosis and treatment are goals which carry the potential for improved prognosis.

Howard Silberman, M.D.
Department of Surgery
UCLA Medical Center
Los Angeles, California 90024

References

1. Morton, D.L., Sparks, F.C. and Haskell, C.M.: Oncology. In Principles of Surgery. S.I. Schwartz, editor-in-chief, New York, McGraw-Hill Book Company, 1974; pp. 303-304, 342.

In vitro susceptibility virtually unchanged

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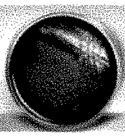
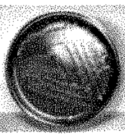
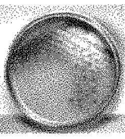
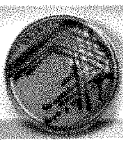
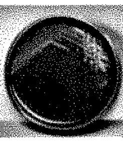
A five-year history of pathogen susceptibility to Garamycin (gentamicin sulfate)—1970-1974

	1970	1971	1972-73	1973-74
Gram-Negative Susceptibility No. of patient tests	97% 8,988*	97% 12,482*	97% 23,382**	97% 25,330**
 *Escherichia coli*	96%	98%	98%	99%
Proteus species, indole-negative	97%	99%	97%	98%
 *Proteus* species, indole-positive	98%	96%	96%	96%
 *Pseudomonas aeruginosa*	95%	95%	94%	94%
 *Klebsiella-Enterobacter-Serratia*	97%	98%	98%	98%
Staphylococcal Susceptibility No. of patient tests	96% 1,550*	94% 1,631*	95% 2,941**	96% 3,268**
 *Staphylococcus aureus*	96%	95%	95%	95%
Staphylococcus, all others	97%	92%	95%	96%

Source: I.M.S. Audit of Pathology Cultures—1970-74.
These *in vitro* data are based on results obtained from hospitals in a nationwide audit. (*100 hospitals reporting; **200 hospitals reporting.) The pathogens tested were obtained from all inpatient and outpatient services.
***In vitro* susceptibility data are not necessarily indicative of clinical effectiveness.**

See Clinical Considerations section which follows...

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>
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>
> **Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.**
>
> **In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.**
>
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>
> **Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.**
>
> **The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.**
>
> **USAGE IN PREGNANCY Safety for use in pregnancy has not been established.**

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

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Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION

GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:
*Patients with normal renal function**

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lbs.), the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

**In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.*

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration, in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused over a period of 1 to 2 hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., is supplied in 2 ml. (80 mg.) multiple-dose vials and in 1.5 ml. (60 mg.) and 2 ml. (80 mg.) disposable syringes for parenteral administration.

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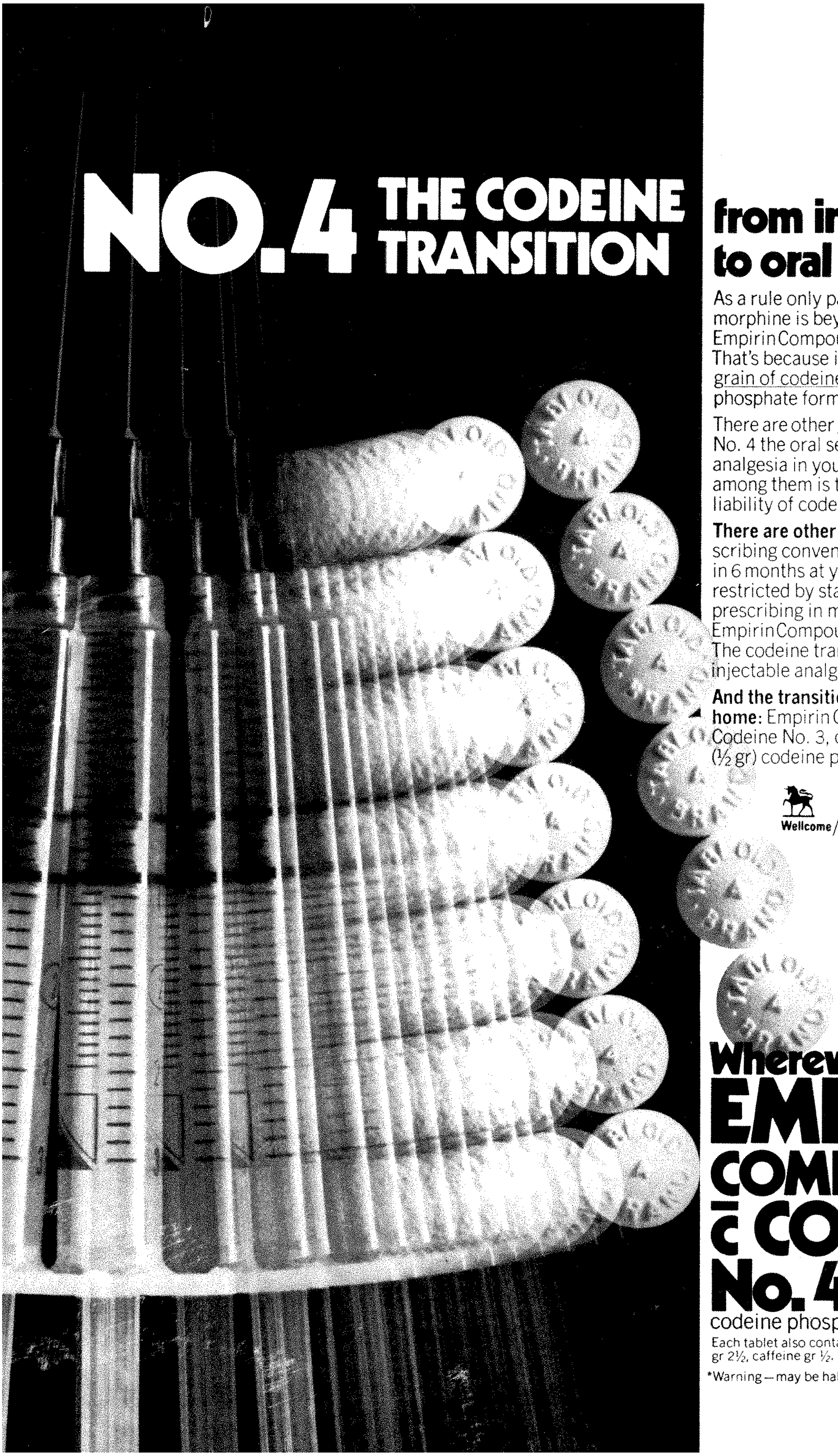

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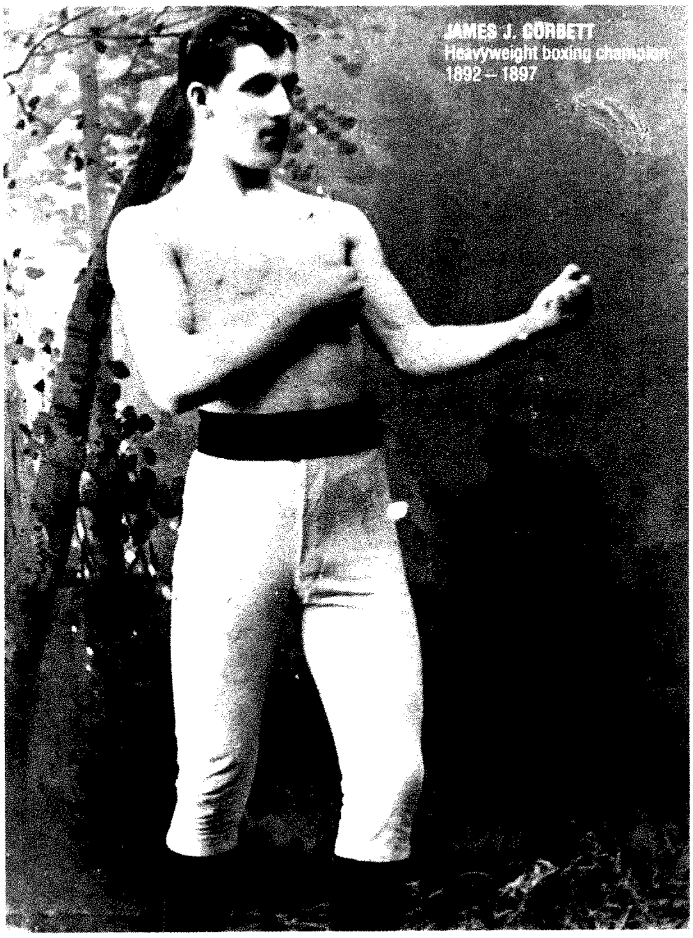

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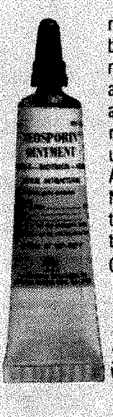

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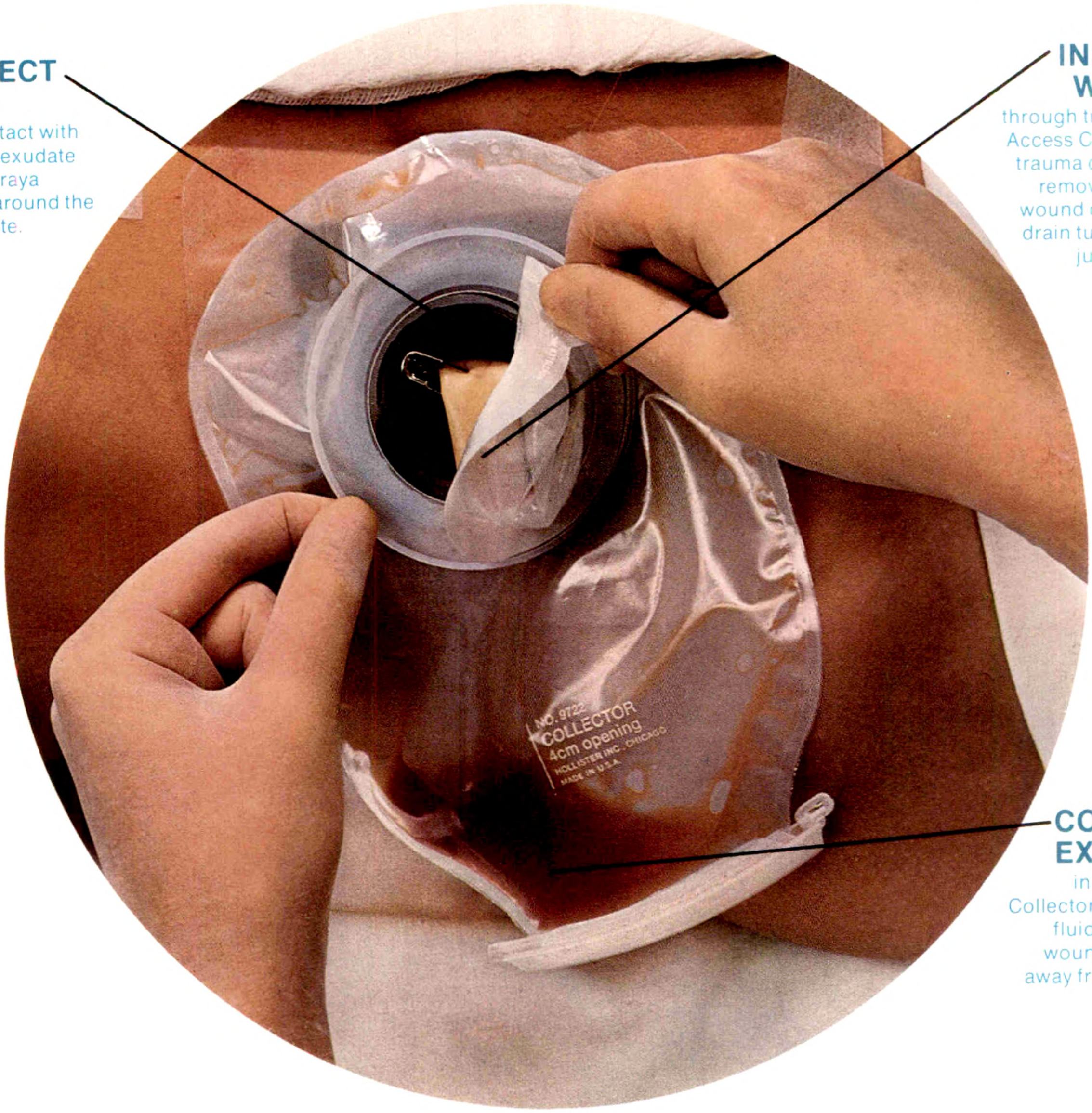

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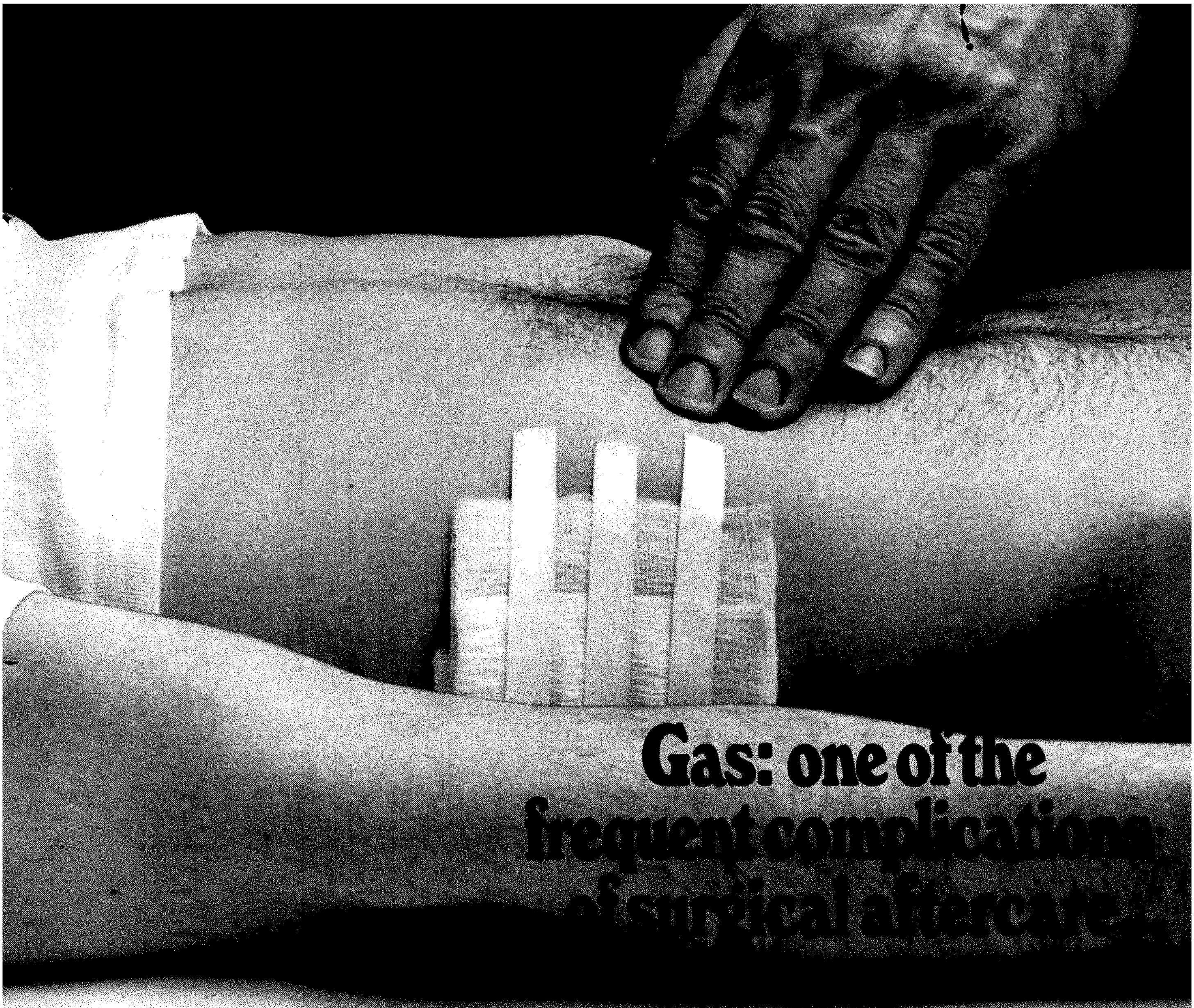
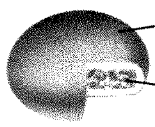


Painful gas accumulation in the gut, due to altered intestinal motility, aerophagia and increased salivation, often complicates surgical aftercare.

To help avoid or dispel the acute discomforts of post-op pain in the gut, Phazyme provides simethicone, *"... an effective, safe and simple method of preventing abdominal distention, gas pain and reducing the incidence of ileus."*[1]*



Phazyme's unique dual-phase action releases 20 mg. of specially-activated simethicone initially to the stomach for immediate dispersion of entrapped gas.

The protected inner core delivers an additional 40 mg. of specially-activated simethicone to relieve pain of entrapped gas throughout the lower G.I. tract.

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And Phazyme is safe ... no systemic effects ... no untoward reactions ... no contraindications other than known allergy to an ingredient.

1. Gibstein, A., *et al.*: Prevention of postoperative abdominal distention and discomfort with simethicone, *Obstet. Gynecol.* *38*:386, Sept. 1971.
*Italics ours.

Phazyme®

Reed & Carnrick/Kenilworth, N.J. 07033

prevents and relieves pain due to entrapped gas

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When pain breaks in... you've got a fast answer.

for fast relief of severe pain..
with Maalox® protection.

Ascriptin

with Codeine

No. 2—¼ Grain Codeine Tablets
No. 3—½ Grain Codeine Tablets
no phenacetin—no caffeine

Two dosage strengths:
No. 2 Tablet—
¼ grain (16.2 mg.) Codeine Phosphate
No. 3 Tablet—
½ grain (32.4 mg.) Codeine Phosphate

...both with five grains of Maalox-protected aspirin.

Ascriptin,® an excellent analgesic, antipyretic, and anti-inflammatory, combined with codeine to give effective relief from severe pain with minimal aspirin-induced gastric distress. Ascriptin with Codeine contains **no phenacetin or caffeine.** Each tablet contains Maalox® (magnesium-aluminum hydroxide) 150 mg.

Indication: As an analgesic for the relief of pain of all degrees of severity up to that which requires morphine

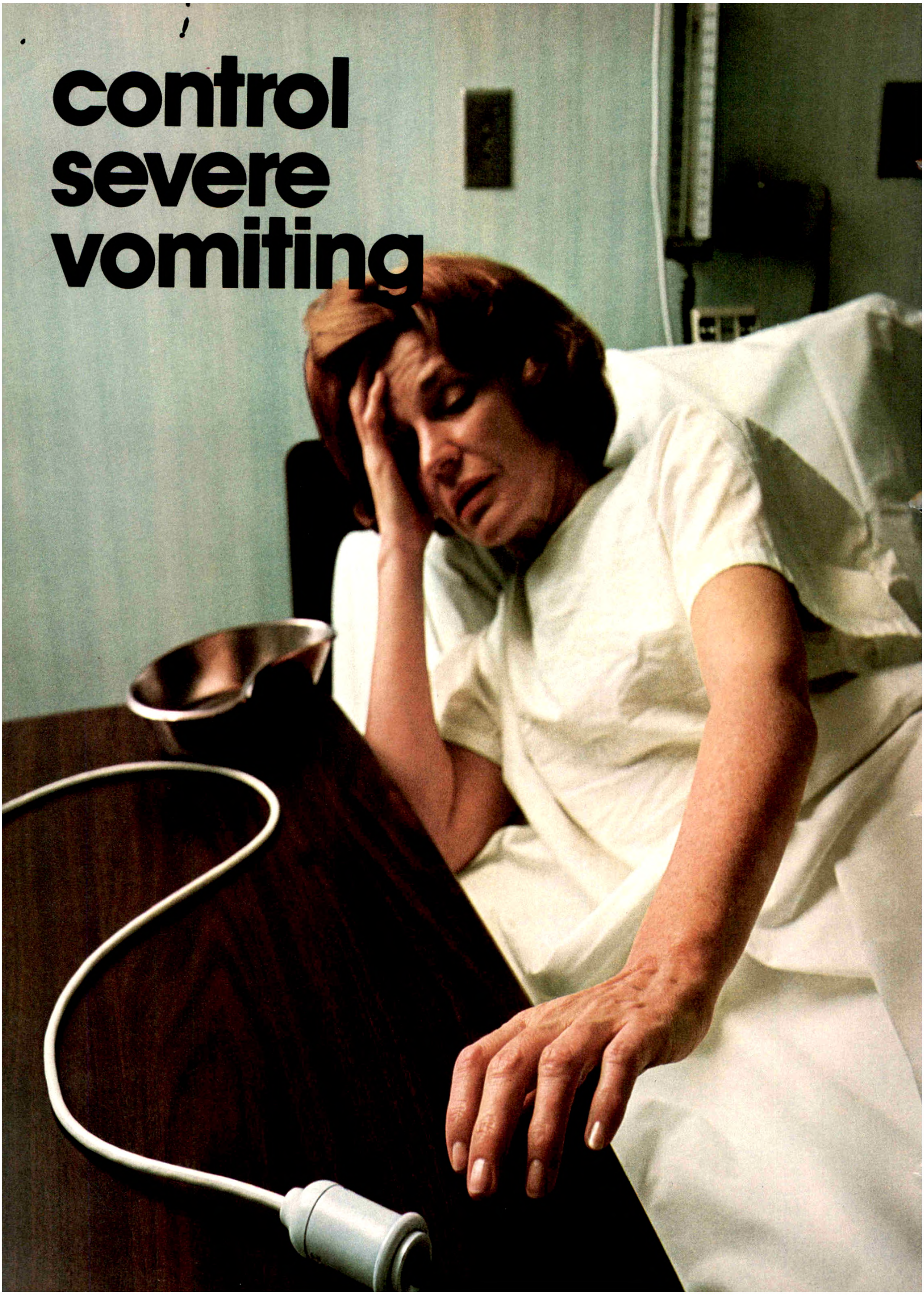
Side Effects: Side effects are rare. Nausea, constipatio and drowsiness may occur.

Warning—may be habit forming.

Usual Adult Dose: Ascriptin with Codeine No. 2 (¼ grain Two tablets every 3 or 4 hrs. when necessary.
Ascriptin with Codeine No. 3 (½ grain): One or two tablets every 3 or 4 hrs. when necessary.

RORER

WILLIAM H. RORER, INC.
Fort Washington, Pa. 19034


control
severe
vomiting

Unsurpassed antiemetic action helps restore normal digestive function so postoperative recovery can proceed smoothly.

11 dosage forms and strengths permit easy administration by parenteral, rectal or oral routes.

'Compazine' is contraindicated in pediatric surgery and in greatly depressed states due to C.N.S. depressants.

The possibility of postoperative aspiration of vomitus should be borne in mind.

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indications

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: To control severe nausea and vomiting. For the management of the manifestations of psychotic disorders.

Possibly effective: To control excessive anxiety, tension and agitation as seen in neuroses or associated with somatic conditions.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants; bone marrow depression; pediatric surgery.

Warnings: Avoid using in patients hypersensitive (e.g., blood dyscrasias or jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days' therapy. Prochlorperazine may intensify or prolong the action of other C.N.S. depressants. Not recommended for children under 20 pounds or 2 years of age.

Use in pregnancy only when potential benefits outweigh hazards.

Precautions: Antiemetic effect may mask toxic drug overdosage or physical disorders. Postoperative aspiration of vomitus has occurred in a few surgical patients who received prochlorperazine as an antiemetic. Deep sleep and coma have been reported, usually with overdosage. **In children with acute illnesses or dehydration, use only under close supervision.**

Adverse Reactions: Drowsiness, dizziness, amenorrhea, blurred vision, skin reactions. Hypotension. Cholestatic jaundice, leukopenia, agranulocytosis. Fatty changes in the liver have been observed in a few patients who died while receiving the drug (no causal relationship has been established). Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, persistent tardive dyskinesia. Contact dermatitis is a possibility with concentrate and injectable forms.

Other adverse reactions reported with Compazine (prochlorperazine, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., severe hypotension in mitral insufficiency or pheochromocytoma).

Grand mal convulsions; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat and organophosphorus insecticides; dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, inhibition of ejaculation; reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; pancytopenia, thrombocytopenic purpura, eosinophilia; biliary stasis; lactation, galactorrhea, gynecomastia, menstrual irregularities, false positive pregnancy tests; photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis; asthma, laryngeal edema; angioneurotic edema, anaphylactoid reactions; peripheral edema; reversed epinephrine effect; hyperpyrexia; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes have been reported, but relationship to myocardial damage is not confirmed. Discontinue long-term, high-dose therapy gradually.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported, but no causal relationship has been established.

Supplied: Tablets—5, 10 and 25* mg., in bottles of 100; Spansule® capsules—10, 15, 30 and 75* mg., in bottles of 50; Injection—5 mg./ml.; Suppositories—2-1/2, 5 and 25 mg.; Syrup—5 mg./5 ml.; Concentrate (intended for institutional use only)—10 mg./ml.; Single Unit Packages of 100 (intended for institutional use only)—5 and 10 mg. tablets; 10, 15 and 30 mg. 'Spansule' capsules.

*For severe neuropsychiatric conditions.

Compazine® Injection 5 mg./ml.

brand of prochlorperazine

the emesis nemesis

Smith Kline & French Laboratories **SK&F**
Division of SmithKline Corp., Phila., Pa. 19101

See next page for summary
of prescribing information.

On the surgical service...

Clinical confidence earned through experience

Keflin® I.V.

cephalothin sodium

2 Gm.* in 100-ml. ampoule

The confidence that comes with 10 years' experience†

Experience with Keflin has established a record of clinical effectiveness in serious skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillin-sensitive and penicillin-resistant), group A beta-hemolytic streptococci, *Escherichia coli, Proteus mirabilis,* and *Klebsiella.*

*Equivalent to cephalothin.

†Keflin became available for clinical investigation early in 1962 and to the profession in 1964.

Brief Summary. Consult the package literature for prescribing information.

Indications: Keflin® (cephalothin sodium, Lilly) is indicated for the treatment of serious infections caused by susceptible strains of the designated micro-organisms in the diseases listed below:

Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli, Proteus mirabilis,* and *Klebsiella*

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy—Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side-effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: Maculopapular rash, urticaria, pain, induration, tenderness, elevation of temperature, reactions resembling serum sickness, anaphylaxis, eosinophilia, drug fever, neutropenia, thrombocytopenia, hemolytic anemia, thrombophlebitis, transient rise in SGOT and alkaline phosphatase, rise in BUN, decreased creatinine clearance, and a positive direct Coombs test have been reported. [020774S]

Lilly

600166

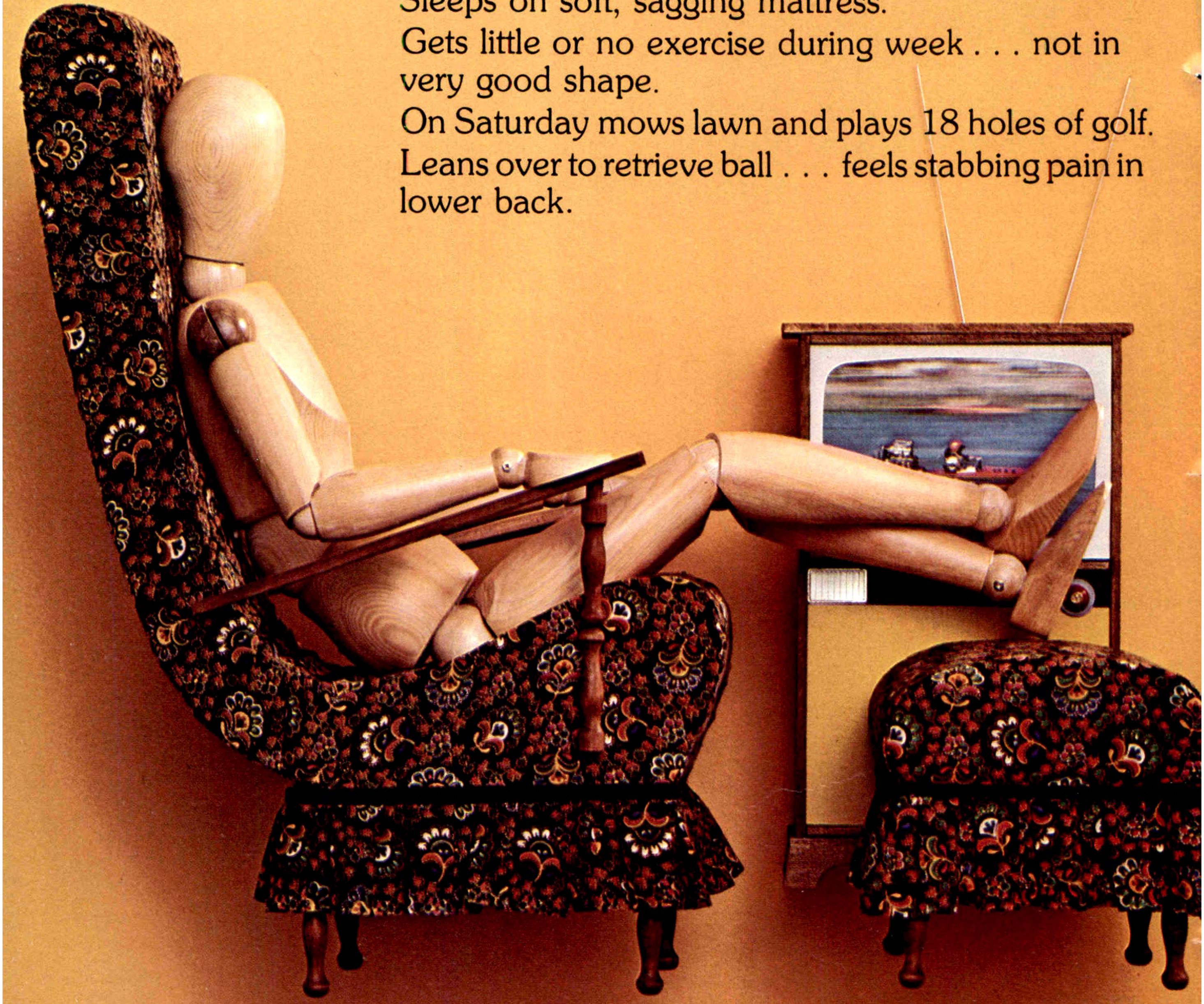
Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

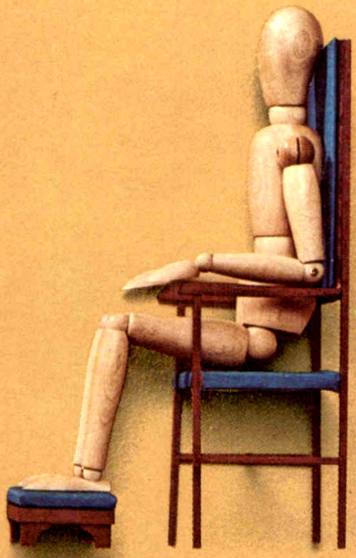
the low-back patient and his problems:

SOFT LIFE 'SUBURBANITE' BACKACHE

Sedentary job. Sits most of day in plush swivel chair.
Sits slumped in overstuffed furniture at home.
Sleeps on soft, sagging mattress.
Gets little or no exercise during week . . . not in very good shape.
On Saturday mows lawn and plays 18 holes of golf.
Leans over to retrieve ball . . . feels stabbing pain in lower back.



the solution:



At work sit in straight chair with firm back . . . knees higher than hips. Prop feet on small footstool to elevate knees. Don't sit in overstuffed furniture. Never sit long in one position . . . get up frequently and move around. Exercise regularly to strengthen abdominal and low-back muscles and help prevent weekend flare-ups. Avoid sudden spurts of vigorous physical activity. A back support can help relieve pain and fatigue.

to relieve discomforts associated with acute, painful musculoskeletal disorders...

ROBAXIN®-750

brand of
methocarbamol 750 mg. capsule-shaped tablets

the Robaxin Regimen:

Complete bed rest on a very firm mattress is usually indicated in the home treatment of acute low-back discomfort. Have patient insert section of plywood ½-¾" thick between mattress and box springs. The use of moist heat is often very beneficial.

Robaxin-750 is often indicated to relieve the discomforts associated with acute, painful musculoskeletal disorders. It is a well tolerated agent which can provide significant relief, usually without serious adverse reactions.

Indications:
As an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Methocarbamol does not directly relax tense skeletal muscles in man.

Contraindications:
Robaxin is contraindicated in patients hypersensitive to any of the ingredients.

Warnings:
Safe use of Robaxin has not been established with regard to possible adverse effects upon fetal development. Therefore, Robaxin should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards.

Precautions:
Safety and effectiveness in children below the age of 12 years have not been established.

It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Methocarbamol may cause a color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) and vanilmandelic acid (VMA).

Adverse Reactions:
Lightheadedness, dizziness, drowsiness, nausea, allergic manifestations such as urticaria, pruritus, rash, conjunctivitis with nasal congestion, blurred vision, headache, fever.

Dosage and Administration:
Initial dosage, 2 tablets q.i.d.; maintenance dosage, 1 tablet q.4h. or 2 tablets t.i.d.

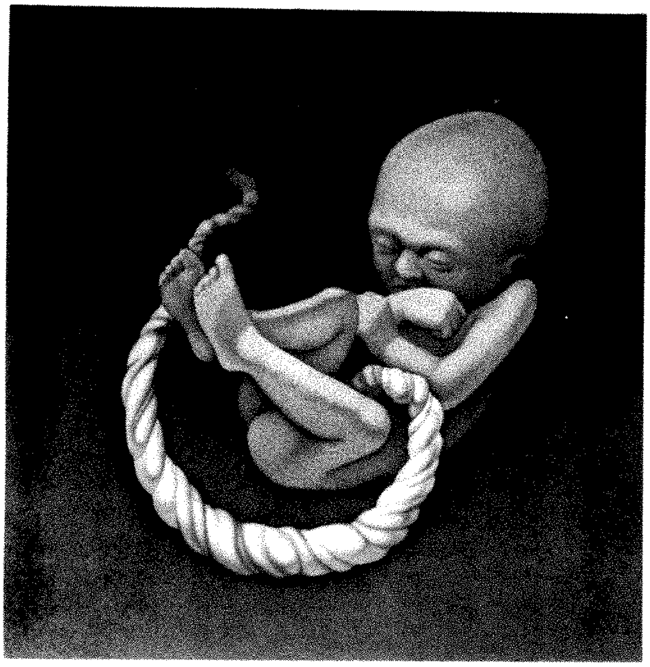
Six grams a day are recommended for the first 48 to 72 hours of treatment. (For severe conditions 8 grams a day may be administered.) Thereafter, the dosage can usually be reduced to approximately 4 grams a day.

Also Available:
ROBAXIN® (methocarbamol) 500 mg.

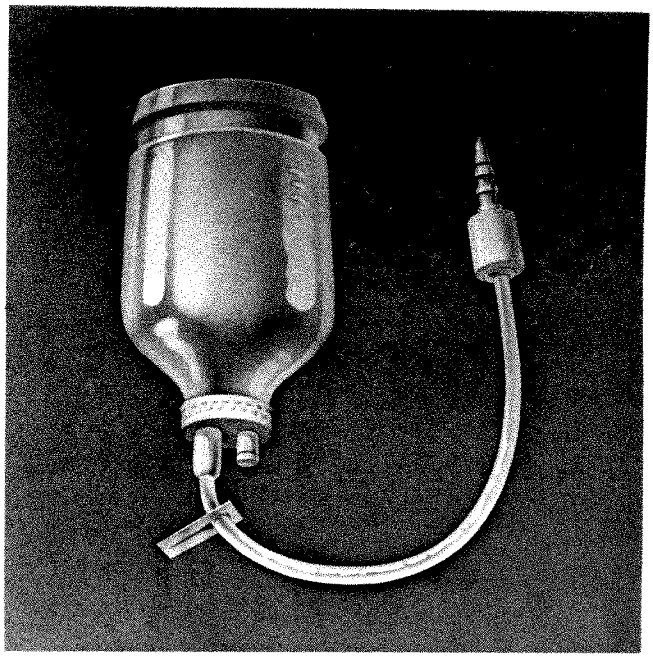
See package insert for full prescribing information.

A. H. Robins Company, Richmond, Va. 23220
A·H·ROBINS

The Lifelines



Total
Parenteral Nutrition



Total or Supplemental
Parenteral Nutrition

Whenever IV nutritional support is indicated, total or supplemental, short-term or long-term,

M.V.I.®

(Multi-Vitamin Infusion)

The comprehensive
multivitamin infusion

Contains C and B-complex
vitamins as well as water-
solubilized A, D and E vitamins

Each 10 cc. ampul[☆] or 5 cc. Concentrate vial[☆☆] provides:

Ascorbic acid (C)	500 mg.
Vitamin A[*]	10,000 I.U.
Vitamin D[*] (ergocalciferol)	1,000 I.U.
Thiamine HCl (B_1)	50 mg.
Riboflavin (B_2)[☆☆]	10 mg.
Pyridoxine HCl (B_6)	15 mg.
Niacinamide	100 mg.
Dexpanthenol	25 mg.
Vitamin E[*] (dl-alpha tocopheryl acetate)	5 I.U.

[☆] With sorethytan laurate 1%, sodium hydroxide 1%; and gentisic acid ethanolamide 2% as preservative.

[☆☆] With propylene glycol 30% as stabilizer and preservative, sodium hydroxide for pH adjustment, and sorethytan laurate 1.6%; in Concentrate as riboflavin-5-phosphate.

[*] Oil-soluble vitamins A, D and E water solubilized with sorethytan laurate; covered by U.S. Patent No. 2,417,299.

BRIEF SUMMARY

INDICATIONS: *in emergency feedings* – Surgery, extensive burns, fractures and other trauma, severe infectious diseases, comatose states, etc. may provoke a "stress" situation with profound alterations in the body's metabolic demands and consequent tissue depletion of nutrients. As a result, wound healing may be impaired, enzyme activity disturbed, hematopoietic tissues affected; hypoproteinemia and edema may appear; convalescence is thus prolonged.

In such patients M.V.I. (administered in intravenous fluids under proper dilution) contributes optimum vitamin intake toward maintaining the body's normal resistance and repair processes.

DIRECTIONS FOR USE: M.V.I. is ready for immediate use when added to intravenous infusion fluids. For intravenous feeding, one daily dose of 10 cc. of M.V.I. or 5 cc. of M.V.I. Concentrate added directly to not less than 500 cc., preferably 1,000 cc., of intravenous dextrose, saline or similar infusion solutions . . . plasma, protein hydrolysates, etc.

PRECAUTION: Allergic reaction has been known to occur following intravenous administration of solutions containing thiamine.

CAUTION: Not to be given as a direct undiluted intravenous injection as it may give rise to dizziness, faintness, etc.

THERAPEUTIC NOTE: Intravenous use should be discontinued as early as practical in favor of an intramuscular or oral vitamin preparation, if deemed advisable.

HOW SUPPLIED: M.V.I.—10 cc. ampuls, boxes of 25 and 100.

M.V.I. CONCENTRATE—5 cc. vials, boxes of 25. Available in 100s only.

USV Pharmaceutical Corp.
Tuckahoe, N.Y. 10707

USV
PHARMACEUTICALS

ANNALS OF SURGERY

Vol. 183 February 1976 No. 2

Functional Evaluation of the Interposed Colon as an Esophageal Substitute

JOHN CLARK, M.B., CHB., F.R.C.S., A. MORALDI, M.D., A. R. MOOSSA, B.SC., M.B. CHB., F.R.C.S.,
A. W. HALL, M.B. CHB., F.R.C.S., T. R. DEMEESTER, M.D., F.A.C.S., D. B. SKINNER, M.D., F.A.C.S.

From the Department of Surgery,
Pritzker School of Medicine,
University of Chicago,
Chicago, Illinois

Five Rhesus monkeys and four human adults with colonic reconstruction of the esophagus have been studied by manometric, fluoroscopic and reflux tests. Transit through the graft is mainly under the influence of gravity. Infrequent colon contractions can be propulsive, and sequential haustral contractions give the appearance of peristalsis. The diaphragmatic hiatus and esophagocolic anastomosis are the sites of weak barriers to reflux which are readily overcome by abdominal compression and gastric distension. Esophageal peristalsis is necessary to return refluxed material and cricopharyngeus muscle is the final barrier to regurgitation.

COLON is generally considered to be a technically reliable esophageal substitute after resection for benign disease. Minor functional inadequacies in colon interpositions are tolerated by the patient who is delighted to be relieved of dysphagia, but regurgitation is sometimes a major problem.

Otherson, Charleston and Clatworthy[5] studied 10 children with colon interposition. None of them could eat or drink rapidly. On fluoroscopic studies barium pooled in dependent parts of the supradiaphragmatic segment and refluxed into the esophagus. The occurrence and significance of peristalsis is in doubt[3,4] and the few manometric studies must be interpreted with caution.[1] Jones[4] and his colleagues demonstrated colonic clearance of acid which stimulates the colon. This is an important protection in the event of gastrocolic reflux especially in the patients who are incompletely vagotomized. It has not been determined whether dietary components stimulate the transplant and aid deglutition. The Standard Acid Reflux Test gives an assessment of gastroesophageal reflux,[8] but Jones et al.[3] found that it could not be performed in patients with colon interposition because a catheter could not be passed into the stomach. A modification of the test in monkeys showed no reflux across the diaphragm.

In the present study a Rhesus monkey model of short segment distal esophageal replacement with colon was chosen to examine more closely the motility pattern of these interpositions and the mechanisms of prevention of reflux and regurgitation. Four human adults were also studied.

Method

Pull through manometry and a modification of the standard acid reflux test were performed in each animal one week preoperatively. Five Rhesus monkeys survived resection of 3 cm of distal esophagus and 2 cm of proximal stomach and "isoperistaltic" interposition of a segment of splenic flexure of colon based on the left colic artery. The stomach was closed transversely with an end-to-end layer gastrocolic anastomosis midway along the suture line. There was no gastric wrap. The esophagocolic anastomosis was performed with two layers of interrupted 4-0 Ethiflex^{R} sutures.

The approach was thoraco-abdominal in three instances and abdominal with division of the diaphragmatic hiatus in two. All animals were vagotomized and a pyloromyotomy was added. Two to 6 months later laparotomy was performed and a thread guide was led from the nose, through the reconstruction and exteriorized through a gastrostomy. One end of the thread was sutured to the nasal septum and the other end fixed to the internal oblique muscle one inch from the gastrostomy. External oblique muscle was closed over the

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Submitted for publication August 29, 1975.

All correspondence: Dr. A. R. Moossa, The University of Chicago, 950 East 59th Street, Box 440, Chicago, Illinois 60637.

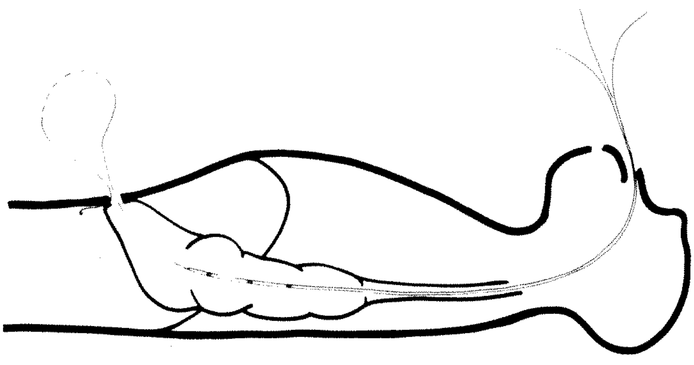

FIG. 1. The position of the manometric catheter and thread during studies.

knot. Studies were commenced a week later. In all but one animal studies occupied from 8 to 14 hours of recording over a period of 4 to 6 weeks.

The Pressure Profile and Motility Patterns

The thread allowed repeated manometric studies on separate days, by static and pull through techniques using a triple lumen (each internal diameter 1.67 mm) Tygon^R tube with a tail inserted as shown in Fig. 1. Three side holes, 3 cm apart, were marked for radiologic studies by a column of mercury distally in each lumen. It was not possible to pass a catheter through the interposition without a guide because the soft saccular colonic wall did not allow the tip to negotiate the diaphragmatic hiatus. The tail ensured that the catheter was not curled and allowed gastric aspiration.

The catheters were perfused with 0.9% saline by a Harvard pump (Model 932) at 0.23 ml per minute per lumen, which avoided excessive fluid loads. Statham P23Db transducers were connected to a Brush 440 direct writing recording system and the chart speed was 125 mm per minute. Zero, balance and calibration were checked before and during each experiment. The animals were lightly sedated with phencyclidine (Sernylan^R 0.75 mg/kg) and lay supine for all the studies except for postural changes during radiography and acid clearing tests. The effect of intraluminal stimulants was studied by injecting solutions 1 cm above the proximal or middle hole along a fine polyethylene tube taped to the manometric catheter.

In 4 patients manometric studies were performed 2 to 3 weeks postoperatively using catheters with side holes 5 cm apart and perfusion rate of 2.29 ml per minute per lumen. In two a thread was passed at the termination of their reconstructive operation and secured to the gastrostomy tube at one end and taped to the nose at the other. The diaphragm was negotiated under fluoroscopy in the other two using a tube with the 3 lumens projecting 10 cm beyond the distal side hole, two filled with mercury and one with the flexible tip of a straight Seldinger arterial guide wire. Tygon^R tubes were stiffened by soaking in isopropyl alcohol for 24 to 48 hours but extra control could be obtained by passing a second Seldinger guide wire down the distal lumen which had been injected with mineral oil.

Radiography

Cineradiography and fluoroscopy with and without simultaneous manometry in the supine, left and right lateral, head up and down positions allowed identification of motility and reflux patterns in the monkeys. The positions of the anastomosis and diaphragm were determined fluoroscopically in all subjects.

The Barrier to Reflux

The manometric profile was obtained with and without the continuous application of 30 mm mercury abdominal compression by a sphygmomanometer cuff. The intragastric pressure was recorded before the cuff was inflated by an air pressure standard (Cordis), and the catheter was withdrawn slowly to the pharynx before deflation. The air pressure standard was calibrated against a mercury manometer and cuff pressure was recorded through a transducer. The site of the barrier to reflux was identified as the point at which the pressure dropped from abdominal to thoracic.

Reflux Tests

In monkeys the catheter was withdrawn to leave the tip of the tail in the stomach, which was aspirated. A pH probe (Beckmann 39042) was inserted into the midsupradiaphragmatic colon. With the reference probe in the mouth, the pH was recorded. Fifty ml 0.1 normal hydrochloric acid was inserted into the stomach before removing the catheter completely. The abdomen was compressed sharply 10 times and reflux was recorded positive if the pH fell below 4 during or after the maneuver. When the pH returned above 5 the compressions were repeated for a total of 10 sets of ten. A score out of 10 was obtained. If the animal failed to clear acid in 5 minutes supine and in 5 minutes in 45° head up position it was scored positive for the remaining sets.

The standard acid reflux test was performed in 3 patients. 300 ml 0.1 N. HCl was placed in the stomach and the pH was recorded 5 cm above the diaphragm while at rest, after three coughs, three deep breaths, a Valsalva and a Muller maneuver. These recordings were made in the supine, right and left lateral and 20° head down positions allowing 20 opportunities to observe reflux, which was recorded if the pH fell below 4.

The pH in the interposition 5 cm above the diaphragm was recorded for 12 hours in the upright and 12 hours in the supine positions. A diet was given containing only foods with a pH between 4 and 7. In one patient a continuous infusion of 0.05 N hydrochloric acid, 100 ml per hour, was given through the gastrostomy to act as a marker for reflux.

Acid Clearing Tests

A bolus of 0.1 normal hydrochloric acid (humans 10 ml, monkeys 5 ml) was introduced alongside the tip of the pH probe in the midsupradiaphragmatic colon, and after the injection the catheter was switched to a pressure transducer. A simultaneous record of pH and contractions was obtained. If the pH remained below 5 after 5 minutes in the supine position the monkeys were placed in a 45° head up position, and the human subjects sat up, for a further 5 minutes.

Regurgitation

Saliva accumulating in the animals' throats was removed periodically by suction. To identify regurgitated gastric content, patent blue dye in 5 ml water was introduced into the stomach via the gastrostomy.

Results

Three weeks after colon interposition all animals ate their normal daily supply of biscuits and none regurgitated. During sedation and handling however, two monkeys regurgitated freely and both ultimately died of pulmonary aspiration despite the routine use of pharyngeal suction. One of these (4081) died after its first manometric study even though pull through traces were obtained without abdominal compression. Its esophagocolic anastomosis was fixed to the diaphragmatic hiatus, but in the others 2.5 to 6 cm of colon lay above the diaphragm, and 4 cm below. Weight loss averaged 1.3 kg 2 to 6 months postoperatively. The threads were tolerated for 8 to 10 weeks.

Esophageal resection was for advanced achalasia and stricture in two patients, peptic stricture in one, and esophageal sarcoma in the fourth. This last patient had a pharyngo-colic anastomosis and could take only very small swallows for fear of regurgitation. She readily regurgitated food taken one or two hours previously. One patient complained of a left hypochondrial ache when she ate a meal of normal size. The remaining two patients were asymptomatic.

Mechanism of Deglutition

With the monkeys in upright position, swallowed barium rapidly passed down the esophagus sometimes without fluoroscopic evidence of peristalsis. Momentary hold up occurred at the esophagocolic anastomosis and then barium dropped under gravity through the colon to arrest above the diaphragm. Small boluses of contrast passed rapidly into the stomach but pooling above diaphragmatic nipping was marked in the two "non refluxing" monkeys (Fig. 2). Drainage continued under gravity interrupted by peak inspiration and slowed as the cologastric cavity filled with contrast and air.

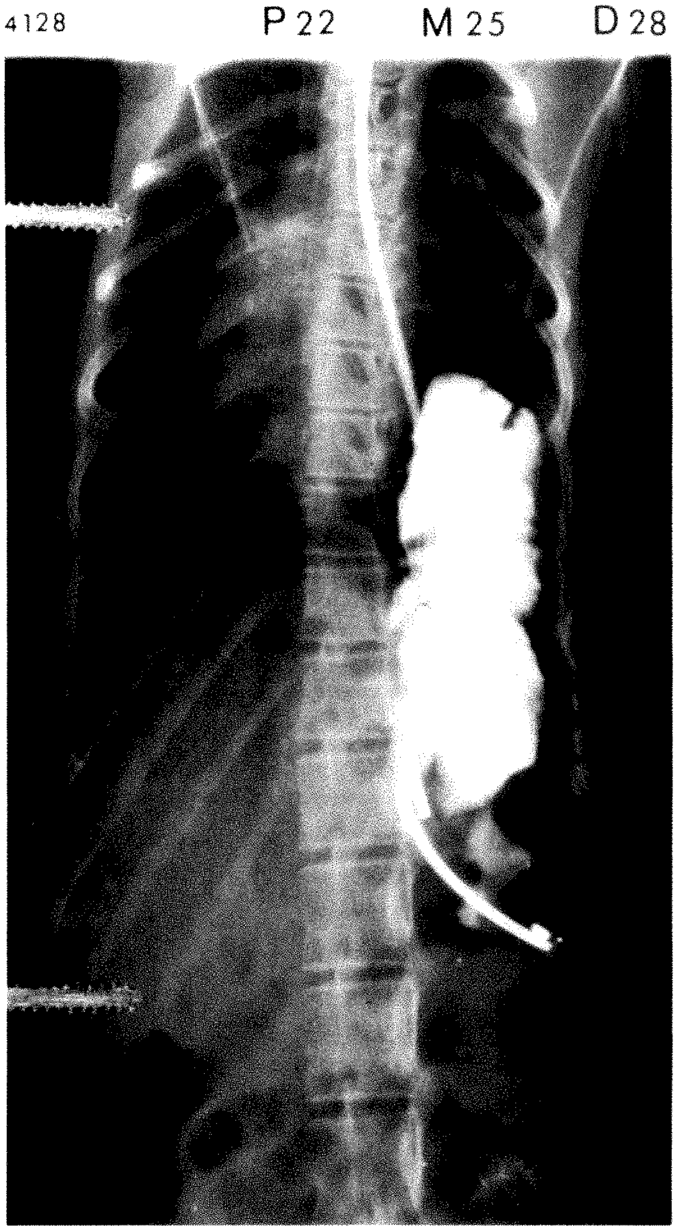

FIG. 2. Supradiaphragmatic pooling of barium in colon interposition. Middle hole of catheter marks diaphragm at 25 cm from nares.

Spontaneous propulsive activity in the colon was difficult to quantify. On separate fluoroscopic sessions, each with a minimum of 30 minutes viewing time, activity was sometimes seen 3 or 4 times, and on other occasions not at all in the same monkey. Haustral, multihaustral and sequential haustral contractions occurred and the movements were completed more slowly than esophageal peristalsis. Contractions in a colon segment emptied it mainly distally but commonly with a little orad reflux. Reflux always occurred freely when there was cologastric distension. No smooth and swiftly progressive waves were seen to propel a bolus through the colon in the manner of true peristalsis.

In the colon adjacent to the esophagocolic anastomosis esophageal peristalsis caused filling with a bolus of contrast resulting in a small pressure rise. This filling wave produced a sequential continuation of esophageal peristalsis into the transplant. With manometry alone it could be mistaken for a contraction transmitted across the anastomosis. It also obscured the point at which esophageal peristalsis first appeared and did not indicate the location of the anastomosis.

Radiologically in two humans the colon segment had minimal evidence of haustration and passage of barium was rapid but in the others haustrations were prominent and barium cascaded from one to the next. Barium pooled in dependent parts and slow haustral contractions were observed to empty the contents into the supra diaphragmatic pool one to four times in 20 minutes. The esophagus was cleared by peristalsis except in the patients with achalasia in whom a fluid level developed as it had done preoperatively. Emptying across the diaphragm occurred intermittently with inspiration and breath holding in maximal inspiration stopped the flow. On one occasion a synchronous multihaustral contraction was seen.

In monkeys and humans intermittent straining and coughing caused the contrast to flow out of the colon segment both upwards and downwards. The patient with a pharyngocolic anastomosis, in whom even slow drinking produced regurgitation, "vomited" the content of the adynamic interposition by rapidly repeated short sharp forceful expiratory efforts.

Stimulated Colonic Motility

The responsiveness to irritant and carbonated beverages was studied by the intraluminal injection of 8 ml of each of 0.1 normal hydrochloric acid (pH 1.0), hot coffee (pH 4.5), whiskey (pH 4.7), Coca Cola^{R} (pH 2.8) and Dulcolax 5 mg in water (pH 7.0). Air (8 ml) and tap water (8 ml) at 37 C were used as controls. Each was applied in random order with aspiration between each and distribution of the studies over three days.

In the four monkeys, 71% (60/85) of the stimuli produced a response in the colon segment. This was synchronous at two or three points 3 cm apart on 53% (32/60) of occasions, segmental (recording in one channel only) in 17% (10/60), and sequential haustral on 32% (19/60). This last form gave a peristaltic appearance on the manometric trace (Fig. 3) but the separation of the peaks was on average 10 · 6 ± 9 · 3 seconds (n = 19). Two of these responses were "antiperistaltic." One animal responded to only 24% (6/25) of the stimuli and contraction occurred twice after the instillation of water. There were no other responses to water or air. In 4 patients stimulation with 0.1 N hydrochloric acid, carbonated drink or coffee produced a sequential multihaustral contraction in 8 and segmental or synchronous contraction in 16 out of 41 tests. The one patient with

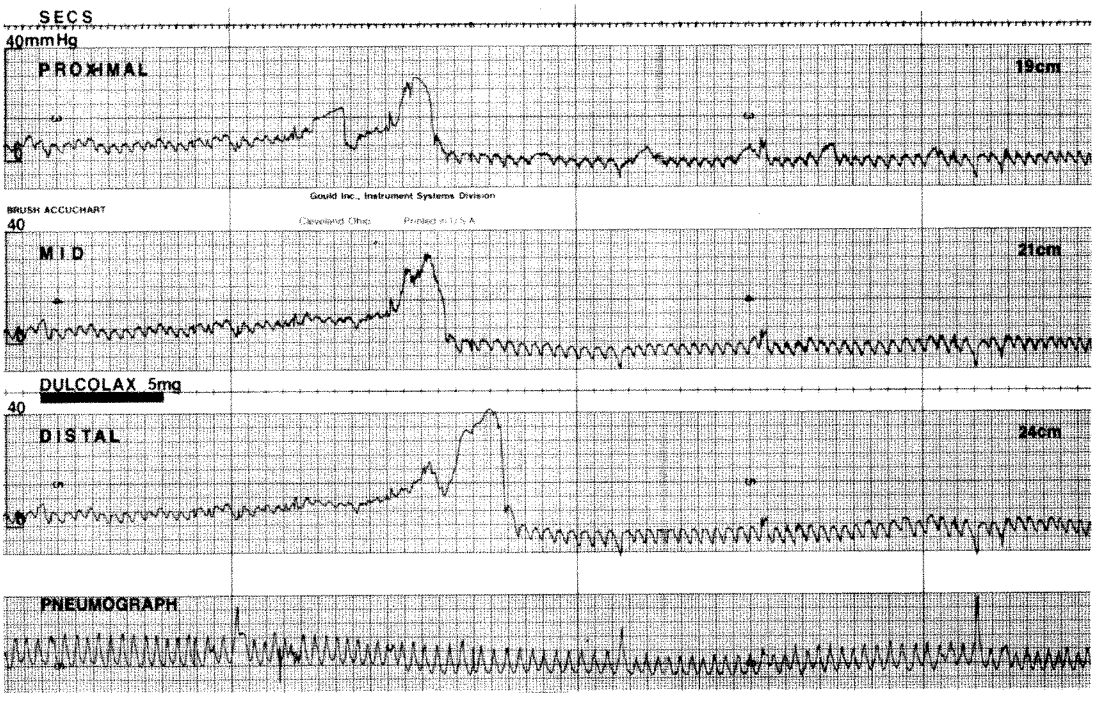

FIG. 3. "Peristaltic" response of supradiaphragmatic colon to 7 ml Dulcolax solution at 18 cm from nares.

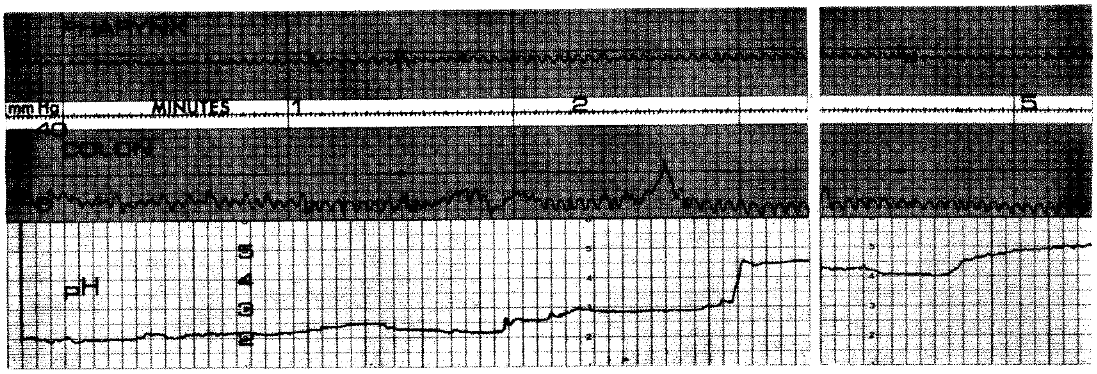

FIG. 4. S.M.A.R.T. Acid clearing from mid thoracic colon with contraction.

pharyngocolic anastomosis regurgitated at the end of the series of tests. In two patients 0.1 N hydrochloric acid produced mild abdominal colicky pain, so severe in one as to terminate the study, and his colonic contractions reached a mean peak pressure of 105.4 mm Hg, 21 seconds duration, and were synchronous in nature.

Acid Clearing Test

There was no clearing of 8 ml 0.1 N hydrochloric acid from the supradiaphragmatic colon in supine monkeys over 5 minutes except in one when a contraction occurred (Fig. 4). When all the animals were tipped 45° head up, the pH rose to above 5 within 3 minutes but fell again when the supine position was resumed. Two patients in supine position cleared colonic acid within 3–7 minutes in a stepwise manner, the pH rising with each swallow. The third failed to clear in 13 minutes supine and took 5 minutes to clear when she sat up. Studies on the fourth patient were aborted for technical reasons.

The Site of the Anti-Reflux Mechanism

On the manometric profile the respiratory inversion point and the pressure drop coincided in 87% of all 195 traces. In the remainder, movements or contractions obscured the respiratory pattern but the first point at which inversion was recognized was an average 0.8 ± 0.5 cm (N = 25) from the pressure drop. In 4 animals the closure point of the lumen was at the diaphragm in 94% (67/71) of non compression traces and in the fifth (3184) at the esophagocolic anastomosis in 90% (35/39). The reason for the changeable position of the closure point is shown in Fig. 5 which is a manometric trace taken from the supradiaphragmatic colon during fluoroscopic observation. This segment recorded abdominal pressure and respiratory pattern up to the esophagocolic anastomosis until a contraction occurred closing the supradiaphragmatic colon for two minutes. During this time, the intraluminal pressure was thoracic and respiratory reversal occurred. The pressure reverted to abdominal with reflux and re-establishment of a common cologastric cavity up to the esophagocolic anastomosis.

The site of the anti-reflux mechnism when intragastric pressure was raised was tested by obtaining the pressure profile with the continuous application of 30 mm Hg abdominal compression. All animals then refluxed and vomited at some time. When a pressure barrier was identifiable, albeit breaking down intermittently, the site

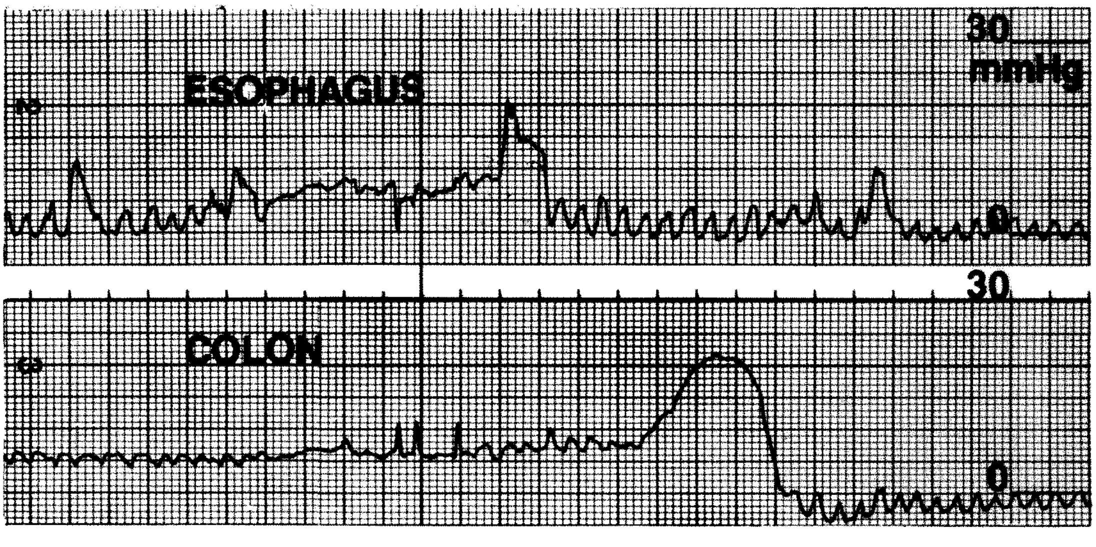

FIG. 5. Esophageal peristalsis preceding colon contraction which empties supradiaphragmatic segment producing drop to esophageal pressure and respiratory reversal.

TABLE 1. *The Incidence of Regurgitation During Pull Through Studies Related to Reflux Status*

Monkey #	S.M.A.R.T.	Non-Compression Traces total #	Non-Compression Traces % with Regurgitation	Compression Traces total #	Compression Traces % with Regurgitation
4113	4/10	27	28%	15	60%
4128	0/10	18	17%	15	60%
3184	10/10	39	0%	36	8%
4123	10/10	21	71%	15	60%
4081	Died of regurgitation and aspiration before tested	9	66%	—	—

was the same as before compression in all but one monkey in which the closure point moved from the diaphragm to the esophagocolic anastomosis indicating that compression had overcome weak diaphragmatic nipping and produced a common cologastric cavity.

Reflux Status

Table 1 shows the scores for each monkey on the standard monkey acid reflux test (S.M.A.R.T.). Even though two were "non-refluxers" all animals refluxed some time during their studies as evidenced by the regurgitation of gastric content and fluoroscopy. The barrier to reflux was readily overcome by abdominal compression and intraluminal distension. Two patients showed no reflux from below the diaphragm and their scores were 0/20. Twenty-four hour pH monitoring on these two did not give an indication of gastric acid reflux because of their vagotomy. The third patient scored 15/20 and he was subjected to 24 hour pH monitoring with gastric infusion of acid. He recorded a pH of less than 4 only 1% of the time. The gastric pH was 2. (The duration of reflux in 7 normal volunteers was 1.5 ± 1.4% of the study time). The mean duration of pH recordings greater than 7 in all three patients was 49% (±15) of their total study time.

Regurgitation

The incidence of regurgitation during pull through studies on monkeys is shown in Table 1. Regurgitation did not occur every time the antireflux barrier broke down. Protection was afforded by esophageal peristalsis in 3 non-compression and 24 compression traces in 3 monkeys. Figure 6 illustrates the manometric appearance of this process during an abdominal compression pull through. The pressure and respiratory pattern are abdominal in the common cologastric cavity. At 19 cm from the nares lay the esophagocolic anastomosis above which swallows repeatedly initiated primary peristalsis which cleared and closed the esophageal lumen down to the anastomosis. The resultant drop to intrathoracic pressure and respiratory reversal lasted 3 to 5 seconds before reflux recurred, and the pressure and respiratory pattern again became abdominal. The esophageal lumen was then open in continuity with the stomach until the next swallow. Fluoroscopy confirmed this sequence of events. With the animals supine and not stressed secondary esophageal peristalsis occurred and cleared the esophagus but reflux from the colon occurred passively immediately after the pressure wave disappeared.

Regurgitation occurred in 70% (21/30) of the non-compression pull throughs in the two animals (4081 and 4123) which died of aspiration. Each had a widely open diaphragmatic hiatus admitting two fingertips.

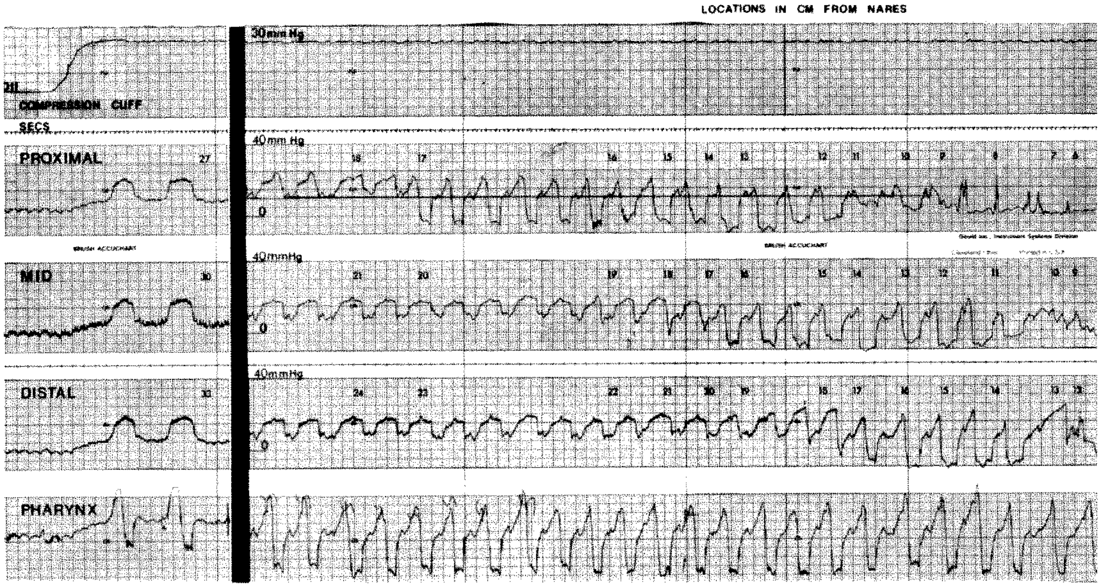

FIG. 6. Abdominal compression—swallows preventing regurgitation.

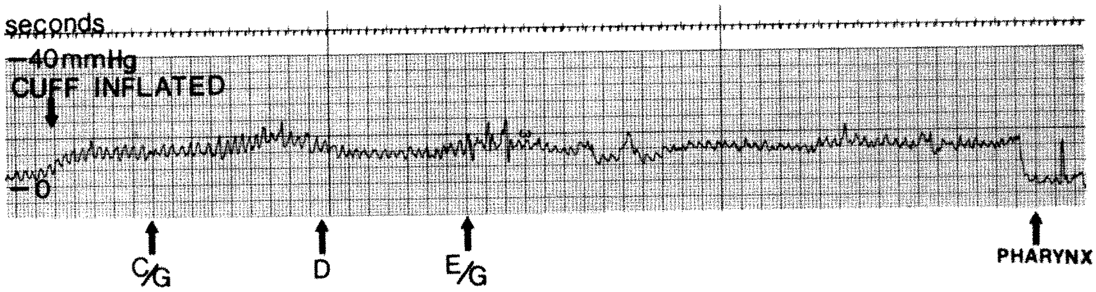

FIG. 7. Abdominal compression. Common cavity up to circopharyngens: c/G = site of cologastric anastomosis; D = site of diaphragm; E/G = site of esophagogastric junction.

Esophageal peristalsis was normal preoperatively but was rare and weak postoperatively and the pattern of clearing of reflux was not seen. In contrast the third animal (3184) with a high reflux score rarely regurgitated and esophageal peristalsis was powerful and frequent. This was the only animal to show cricopharyngeus muscle preventing regurgitation during compression studies. Fig. 7 shows one of 9 similar traces. The gastric pressure rose with inflation of the abdominal cuff and this level was maintained through to cricopharyngeus muscle without respiratory reversal. Cricopharyngeus and the upper 5 cm esophagus were the only protection against regurgitation in the two patients with achalasia.

During the intraluminal stimulation tests two animals regurgitated and two did not. Three "isoperistaltic" multihaustral and 7 synchronous contractions produced regurgitation.

Discussion

Confusion over motility patterns in colon has not been confined to transplants. Bayliss and Starling in 1900[2] were the first to point out that manometry alone did not indicate the presence or type of movement occurring. In 1962, Ritchie et al.[6] combined open and balloon tip catheter manometry with synchronized cineradiography in humans. In the right colon haustral contractions delayed the flow of chyme arriving intermittently from the ileum. Movement of liquids occurred along low pressure gradients following contractions. The chance sequential occurrence of pressure rise in adjacent segments did not indicate peristalsis which is a progressive propulsive front of high pressure preceded by a low pressure zone. This he saw only once in 200 examinations. Because of the infrequency of propulsive movements time lapse cineradiography was more informative about left colonic patterns. Spontaneous and stimulated motility was mainly haustral and multihaustral. Retropulsion was common especially under carbachol stimulation, and even propulsive contractions often allowed a little orad leakage. The type of activity and direction of flow depend on the nature of the colonic content, the proximal input and the resistance to egress distally.[9]

Our studies indicate that propulsive waves in the transplanted colon are rare and they contribute very little to the speed and efficiency of deglutition. They confirm that transit and stagnation in the graft is gravity de-

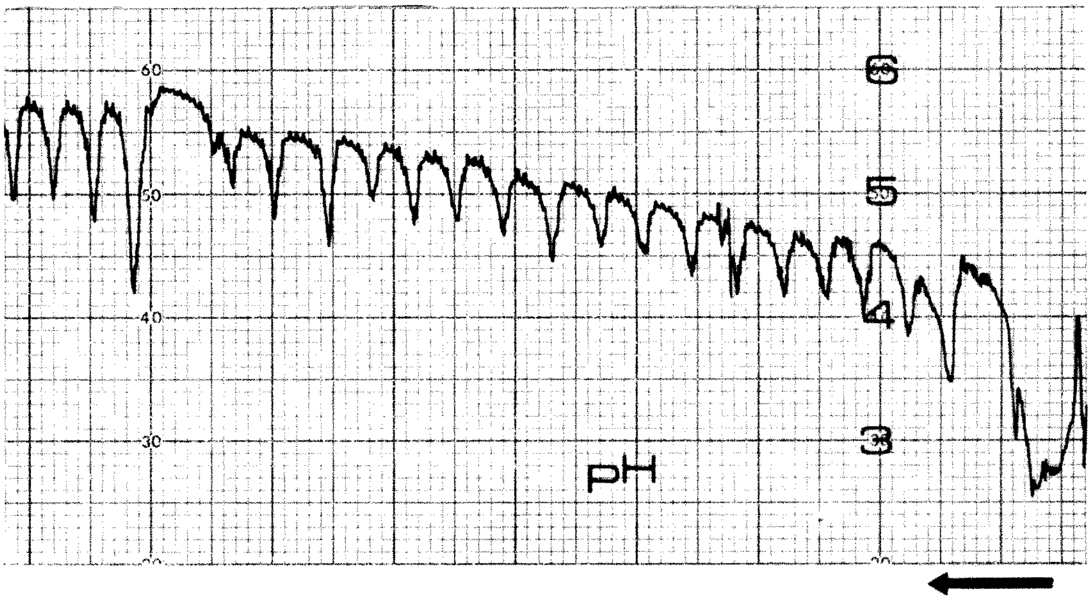

FIG. 8. Standard acid reflux test showing fluctuation in pH record with respiration in man during reflux of acid into supradiaphragmatic colon.

pendent and that occasional contractions can aid emptying. The result of stimulation with an aperitif, coffee, carbonated beverage or even Dulcolax in solution may help relieve symptoms of stasis, but there is a risk of regurgitation of pooled material. Esophageal peristalsis and gravity are the only consistent motive forces and the maximum length of functioning proximal esophagus should be preserved. Passive flow of barium in monkey and man occurred intermittently with each inspiration. At this point in the respiratory cycle the abdomino-thoracic pressure gradient is greatest and relief of diaphragmatic occlusion is necessary to allow flow under gravity.

Reflux can be controlled weakly and variably at the diaphragmatic hiatus and esophago-colic anastomosis and is readily overcome by raised intraluminal pressure and distension. This was observed radiologically and explains the high reflux score in one patient when the stomach was loaded with acid, but little acid reflux during prolonged pH monitoring with a slow intragastric acid infusion. During standard acid reflux testing the recorded pH fell 0.5 unit with inspiration and rose with expiration in this patient (Fig. 8). Washing back and forth was observed with respiration in the monkeys when barium distended the cologastric cavity.

Tightening of the hiatus may reduce reflux but risks compression of the vascular pedicle and delayed emptying of the supradiaphragmatic colon. A complete gastric wrap around the distal colon segment is rarely possible but the anti-reflux effect of a low posterior gastro-colic anastomosis needs study. The technique of one of our authors (D.B.S.) is to suture the remaining fundus to the hiatus anteriorly so producing an incomplete wrap. In the supine position fluid content flows towards the pharynx and esophageal peristalsis is the most important factor in returning it. If colonic contractions are stimulated, clearing or reflux may be enhanced, and in the absence of either mechanism cricopharyngeus muscle provides the final protection against regurgitation. Twenty-four hour pH monitoring of the supra-diaphragmatic colon revealed prolonged periods of alkaline recordings. This may be due to colonic secretion of mucus which could be a protection against reflux colitis. Bile reflux as a factor has not been evaluated.

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Historical Aspects in the Development of Venous Autografts

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During the past 75 years much progress has occurred in the field of vascular surgery. During this period, contributions from clinical surgeons have stimulated new scientific discoveries which have led to further clinical applications in a mutually perpetuating cycle of surgical advancement. One of the major achievements has been the use of the venous autograft employed as an arterial substitute. First used by Goyanes in 1906 to replace a popliteal aneurysm, a venous autograft was first successfully employed in the United States by Bernheim in 1915. The stepwise development of this aspect of modern vascular surgery is presented, and the role of other related contributions in making its use feasible is reviewed.

IN THE PROGRESS of vascular surgery, the events between 1888 and 1967 represent the period of most significant development. Beginning with Matas' introduction of endoaneurysmorrhaphy[16] and extending to the popularization of vein grafts to bypass coronary artery obstructions by Favaloro,[6] this interval is characterized as one of remarkable achievement. Why was this period marked by such ferment? Was it the result of a technical advance which suddenly opened new horizons? Was it simply part of a generalized acceleration in medical progress which began at the turn of the century and is still going on today? The answers to these questions provide a lesson in the importance of history to medicine and represent a study in the absolute interdependence of basic and clinical research.

For centuries, surgeons had brought the techniques of amputation, incision and drainage to bear on problems not amenable to "diet or drugs." With the advent of anesthesia and antisepsis, however, a new group of problems arose demanding the surgeon's attention. The philosophy of *removal* began to be supplanted by the concept of *repair*. This was nowhere more apparent than in the nascent field of vascular surgery, where simple ligation of an injured vessel often entailed significant tissue loss secondary to gangrene. In the presence of an aneurysm, there was the additional danger of rupture and almost certain death from hemorrhage, since collateral vessels frequently supplied the aneurysm and were not included in the usual ligation procedure. Therefore, when Rudolph Matas (Fig. 1) reported the technique of endoaneurysmorrhaphy in 1902, 14 years after his first clinical application of the procedure,[16] a great advance was achieved. The method was most effective in preventing recurrence of the aneurysm; however, it did interrupt normal circulatory pathways and the incidence of gangrene, though low (5–7% in Dr. Matas' hands), was nevertheless troublesome.

The next logical step was resection of a segment of artery and primary reanastomosis of the severed ends. This was accomplished in 1895 by Zoege von Manteuffel,[15] and in the following year Murphy of Chicago achieved the first successful repair of an arteriovenous fistula-aneurysm with restoration of normal circulatory pathways.[19] Although this approach was simple, elegant and permitted maintenance of vascular continuity, considerable problems occurred with thrombosis at the suture line. The large needles, bulky suture materials and techniques previously quite serviceable in general surgery were inadequate in the delicate and exacting world of blood vessels. Isolated clinical reports indicated that extensive vascular reconstruction was a possibility. It required the landmark contributions of laboratory scientists, however, to overcome the technical problems barring its widespread application. Although there were numerous contributors to this work, the names of Stich, Jaboulay, Murphy, Carrel and Guthrie are preeminent, and that of Alexis Carrel is the most impressive. Through

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FIG. 1. Rudolph Matas, 1860–1957. Matas' endoaneurysmorrhaphy constituted the first major advance in the treatment of aneurysm since the days of Antyllus.

painstaking basic research spanning the decade beginning in 1901, Carrel (Fig. 2), working first with Morel at Lyons University and later with Guthrie at the University of Chicago, laid the foundations of modern vascular suturing techniques, as well as pioneering the field of tissue and organ transplantation. The principles of his technique remain as sound today as when he first described them, almost 70 years ago:

> . . . The results of the present blood-vessel surgery will be enhanced by the use of our methods of temporary hemostasis, of (gently) handling the vessels, of washing them with isotonic sodium chloride solution, of impregnating the threads and coating the vascular wall with vaseline, of exactly approximating the internal layers without invagination, and of suturing with very fine needles while the wall is somewhat stretched.[4]

The work of Carrel and Guthrie was widely reported in the world medical literature and Carrel was honored in 1912 with the Nobel Prize for Physiology and Medicine. Important clinical advances followed closely on the heels of Carrel's discoveries. In June of 1906, Jose Goyanes of Spain (Fig. 3) performed what was to this author's knowledge the first successful interposition of a venous graft for an aneurysmal arterial segment in man.[9] Well versed in the experimental work of Jaboulay,[12] Carrel, Murphy and others, Goyanes provides a brief history of vascular surgery and suturing techniques in his two-part paper and credits his teacher, Professor San Martin, with the concept of substituting a venous graft for an excised segment of artery. In the first section of his paper, Goyanes reports a fascinating case in which he transected the iliac artery and anastomosed it to the iliac vein, which had been ligated proximally. The femoral vein just above the knee was then divided and the proximal end anastomosed to the distal femoral artery, thus bypassing the area of arterial obstruction in the upper thigh. The procedure appears to have been at least temporarily successful in restoring circulation to the lower leg, although extensive followup is not given. In the second section of his paper, Goyanes reports the case of a 41-year-old candymaker who had developed a syphilitic aneurysm of the popliteal artery over a five month period. On June 12, 1906, Dr. Goyanes removed the aneurysm and, since approximation of the severed vessels was not possible, a segment of popliteal vein was excised and used as a graft connecting the severed ends of the artery. Although the patient sustained a postoperative wound infection (probably secondary to gelatin which was injected into the popliteal space preoperatively in an attempt to encourage scar formation around the aneurysm), he eventually recovered with preservation of circulation in the extremity. Goyanes published this report in *El Siglo Medico*, a weekly medical bulletin which was not widely read outside Spain, and therefore the achievement went largely unnoticed. Within

FIG. 2. Alexis Carrel, 1873–1944. For his basic contributions to the field of vascular surgery, Carrel was awarded the Nobel Prize in Medicine and Physiology in 1912.

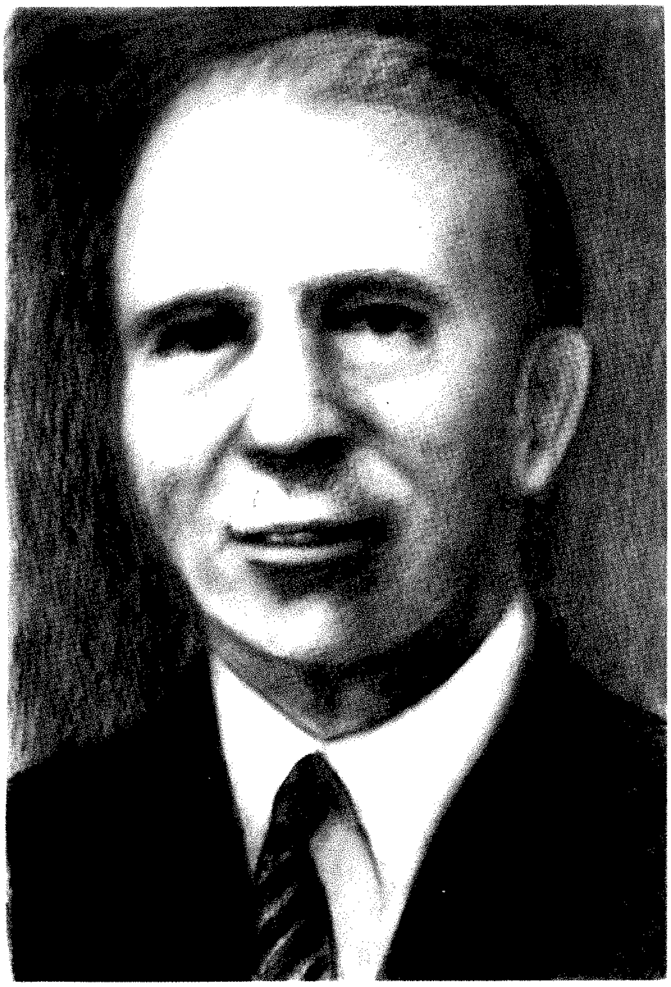

FIG. 3. Jose Goyanes, 1876– . In 1906, Goyanes reported the first use of an autologous vein graft as an arterial substitute in man.

6 months, however, Erich Lexer (Fig. 4), Professor of Surgery at Königsberg, faced a similar problem. He, too, was familiar with the experimental work of Carrel, Murphy and of Stich, for whom Lexer had particular esteem. The patient was a 69-year-old man who had suffered a subcoracoid dislocation of the shoulder 9 weeks previously. An attempt to reduce the dislocation had resulted in an injury to the axillary artery and the formation of a large false aneurysm in the axilla. Several months before, Lexer had been successful in resecting a popliteal aneurysm with primary reanastomosis of the artery using a modification of Payr's magnesium vessel prosthesis. When confronted with a hiatus of some 8 centimeters between the severed ends of the axillary and brachial arteries, however, Lexer recognized that a primary anastomosis was not possible. Fearing that the size and traumatic etiology of the aneurysm had not allowed development of adequate collateral flow to sustain the arm if the artery were simply ligated, Lexer chose to apply the experimental work of Stich[23] to this clinical case. A segment of the greater saphenous vein some 10 centimeters in length was removed from the patient's leg and used to join the ends of the bisected axillary artery. Although the graft functioned beautifully, the patient died of delirium tremens on the fifth postoperative day. Lexer performed the postmortem examination himself and noted that the graft was patent. Although there was a small, non-occluding thrombus on the inner wall of the axillary artery where a clamp had been applied, the suture lines were free of thrombus. Lexer reported this patient at the Thirty-sixth Congress of the German Society for Surgery in April 1907, and published it in that same year in the prestigious *Archiv für klinische Chirurgie*.[13] The journal was read assiduously by a number of prominent surgeons in the United States, as well as virtually the entire European surgical community. Among those Americans who read Professor Lexer's article was William S. Halsted, Professor of Surgery at the Johns Hopkins Hospital and generally recognized as the foremost scholar of American surgery. Halsted was an admirer of Lexer, as he was of German surgeons in general, and he suggested to his associate, Bertram Bernheim, that he pursue this technique experimentally in animals. Bernheim (Fig. 5), son of a wealthy Kentucky distilling family, had graduated from Johns Hopkins Medical School in 1905, after which he had chosen to

FIG. 4. Erich Lexer, 1867–1937. An early genius in the field of reconstructive surgery, Lexer independently demonstrated the feasibility of venous arterial grafts within a year of the report by Goyanes.

FIG. 5. Bertram M. Bernheim, 1880–1957. Though always in the shadow of Halsted and Cushing, Bernheim made important contributions in the areas of blood transfusion and vascular reconstruction. He was the first American to substitute a segment of vein for an artery in man.

spend a period of 18 months in Germany working in hospitals in Baden, Freiburg and Berlin. Returning briefly to his home in Kentucky, Bernheim felt the need of further surgical training and applied to Dr. Halsted for a position. Halsted afforded him the opportunity of working in the Hunterian Laboratory under the direction of Harvey Cushing. Acting upon Dr. Halsted's suggestion that he attempt to duplicate Lexer's work in the laboratory, Bernheim soon found he had an affinity for meticulous vascular work. In 1909, Halsted called upon Bernheim to attempt a long venous graft (12–14 cm) to repair a defect in the popliteal artery created by removal of a sarcoma in the popliteal space. In this case the graft failed because of thrombosis; however, Bernheim continued his work and by 1913 was able to publish an authoritative monograph on vascular surgical techniques, in which he made significant early contributions.[1] Bernheim apparently achieved recognition as a vascular surgeon because of this monograph, and in August 1915, a patient was referred to him by Dr. William Bruce of Sydney, Nova Scotia. The patient was a 43-year-old man who had over the course of three months developed a painful swelling in the right popliteal fossa. The patient had a history of syphilis and his Wassermann reaction was positive, so the presumed diagnosis was a syphilitic aneurysm of the popliteal artery. Before operating on the patient, Bernheim performed the Moszkowicz test,* the results of which indicated that insufficient collateral circulation had developed to prevent loss of the leg if permanent interruption of the popliteal blood flow proved to be necessary.

On the morning of September 3, 1915, at the Union Protestant Infirmary in Baltimore, Bernheim exposed the aneurysm "prepared to do any operation that might be indicated."[2] It was necessary to remove some 15 cm of popliteal artery, which he replaced with a 12 cm segment of saphenous vein. The patient enjoyed an uneventful recovery, and Bernheim presented the case before the Johns Hopkins Hospital Medical Society on October 18, 1915, where it received great acclaim from Dr. Halsted. Other cases followed, and the concept of vascular reconstructive surgery was on its way to becoming a reality.

During the next 20 years (1915–1935), the last remaining obstacles to the development of vascular surgery as a

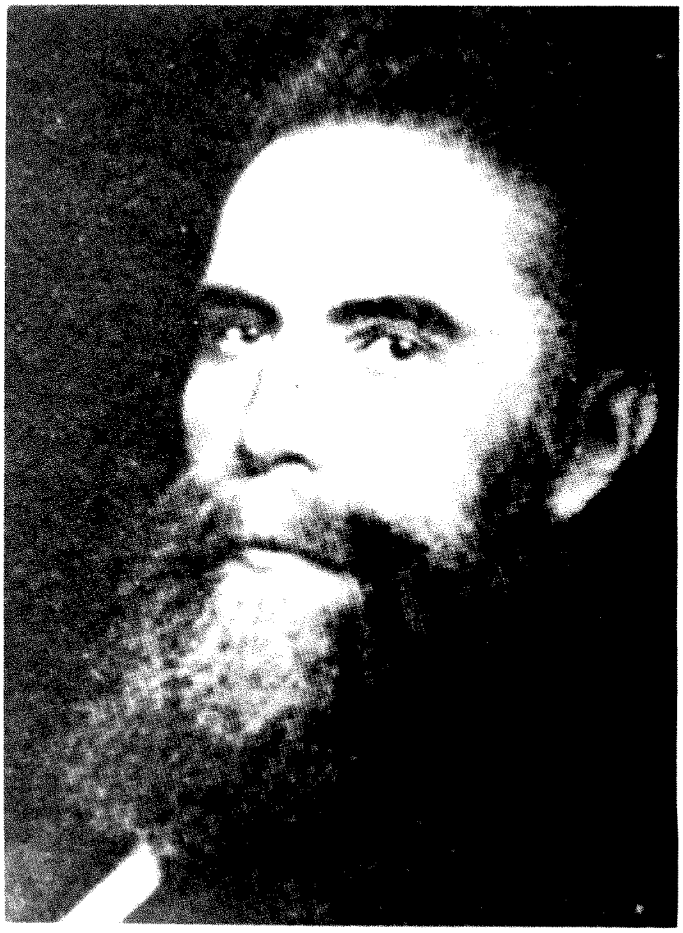

FIG. 6. Wilhelm Konrad Röntgen, 1845–1923. Discoverer of gamma radiation, Rontgen was awarded the Nobel Prize in Physics for 1901.

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* A clinical test used to assess the extent of collateral circulation in an extremity.[17]

full-fledged discipline were overcome. These obstacles centered on the problems of accurate preoperative diagnosis and prevention of thrombosis in the intraoperative period. With aneurysms of the extremities, diagnosis posed no particular problem, for the site of the pathological lesion was clinically manifest. In the case of atherosclerotic lesions, which were considerably more common than aneurysms, there were no surface indicators of the precise location of the lesion. The problem was a difficult one and required the birth of a completely new clinical science to overcome it.

On November 8, 1895, a relatively obscure physicist performing basic research at the Institute of Physics, Würzburg University, first observed the new rays which were to become a cornerstone of the diagnostic armamentarium in virtually every branch of medicine.[20] The man's name, of course, was Wilhelm Konrad Röntgen (Fig. 6), and in his discovery lay the key to accurate diagnosis of vascular lesions. In 1918, D. F. Cameron published a paper on the use of iodide salts as a contrast medium in roentgenography.[3] This work stimulated Sicard and Forestier who are credited with the development of an iodized poppyseed oil (Lipiodol) which was the first vascular contrast medium to be used in humans.[21] With Forssmann's report of the first successful cardiac catheterization in 1929,[7] virtually every segment of the vascular circuit was opened to diagnostic examination.

The solution to the problem of thrombosis lay in basic research, and the man who almost single-handedly solved it was William Henry Howell. Born in Baltimore and a product of Johns Hopkins, Howell and Jay MacLean, a medical student working in Howell's laboratory, happened upon an anticoagulant which they extracted from liver while trying to isolate thromboplastin.[14] Howell named this substance "heparin,"[11] and with the discovery by Charles and Scott of a means for large scale extraction of heparin from beef liver and lung in 1933,[5] the problem of intraoperative thrombosis was solved.

While basic and clinical research was providing the means for peripheral vascular surgery, the World Wars demonstrated the need. According to Matas, one-fourth of the wounded treated at the front in World War I required special attention for injuries of the blood vessels, and at the base hospitals 2% of the wounded were admitted for the treatment of traumatic aneurysms.[18] If the first World War demonstrated the need, it also demonstrated the fact that most surgeons were inadequately trained in vascular techniques to fill that need. The improved results obtained in the treatment of vascular combat injuries in World War II and the Korean War were attributable to several factors, among them better evacuation methods, improved treatment of hemorrhagic shock, blood banking and the advent of antibiotics. In large part, however, this was a result of increased skill and better training in vascular surgical techniques.

After the War, experience gained in the management of traumatic lesions was applied to the problem of acquired obstructive disease. In 1950, Holden reported the use of a saphenous vein to bypass an atherosclerotic femoral artery occlusion, with prior angiographic demonstration of the site of the lesion.[10] In the following year, Voorhees, Jaretzki and Blakemore opened further the horizons of vascular surgery with their report of a synthetic substitute for blood vessels, Vinyon "N."[24] Although this original graft material did not withstand the test of time, its descendants are now a mainstay of vascular reconstructive operations everywhere.

The remaining achievement of this extraordinarily productive period in the history of vascular surgery was a logical extension of the techniques of catheterization and vein grafting. In 1958, at the Cleveland Clinic, Sones successfully performed *selective* coronary angiography, allowing for the first time antemortem correlation of electrocardiographic and hemodynamic parameters with specific alterations in myocardial perfusion.[22] The logical extension of this work was the application of vein grafting techniques to the coronary circulation. In Baltimore in 1962, a 41-year-old patient who had had a previous right coronary endarterectomy for angina pectoris returned with recurrence of symptoms. Coronary arteriography was performed and demonstrated complete occlusion of the previously endarterectomized segment. Faced with the obvious shortcomings of the endarterectomy technique on the one hand and on the other with the incapacitating symptoms of the patient, Sabiston performed an aorta-to-right coronary artery graft using an autologous saphenous vein. Unfortunately, the patient suffered a cerebrovascular accident in the postoperative period and expired three days later. At autopsy, thrombus was present at the aortic anastomosis, and this was the presumed source of the fatal stroke. This complication discouraged further pursuit of the technique at that time.

In 1964, Garrett and associates at Baylor performed a successful graft from the aorta to the left coronary artery and demonstrated patency 7 years later.[8] The pioneering work of Rene Favaloro established the aorto-coronary bypass graft as a feasible procedure.[6] This work was accomplished at the Cleveland Clinic, where Sones had earlier perfected the diagnostic technique of selective coronary arteriography almost a decade before. The significance of this advance is indicated by the fact that over *half* of the procedures in which cardiopulmonary bypass was used in 1972 involved vein grafts to the coronary arteries.

There have been many contributors to the field of vascular surgery whose work has been omitted from this brief survey only because a complete coverage of the subject would be impossible except in a major work. The justification for choosing the contributors and events of this particular period lies in the fact that this represented a time of accelerated progress and, more importantly, that it is a classic example of the symbiotic relationship between basic and clinical research. This latter point is in danger of being forgotten in the current period of increased demand for "clinical relevance" in the allocation of our research support and efforts. Yet clinical investigation without basic research grows rapidly sterile, and basic research without clinical application becomes rapidly impotent. That this interplay between the research laboratory and the clinical situation is a *sine qua non* for medical progress is one of the lessons of history. The development of vascular surgery is clearly a striking example.

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The author wishes to thank Mrs. Bertram Bernheim for contributing biographical information concerning her husband, Professor Bernheim. Thanks are also due Kaye Townsend and Sandra Justice for assistance in preparing the manuscript.

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Attempted Retrograde Cannulation of the Ampulla:

A Probable Cause of Mass in the Pancreas

G. P. BLOOM, M.D.,* D. FROMM, M.D., S. ROSENBERG, M.D., H. GOLDMAN, M.D.

Two patients developed a focal mass in the head of the pancreas presumably following attempted endoscopic retrograde cholangiopancreatography (ERCP). These lesions grossly mimicked carcinomas of the pancreas. In one case a radical pancreatoduodenectomy was performed because of the misleading gross findings. A focal mass in the pancreas following ERCP may develop due to asymptomatic pancreatitis caused by the procedure.

RETROGRADE CANNULATION of the common bile and pancreatic ducts has become an established procedure for the diagnosis of extrahepatic biliary obstruction and possibly pancreatic diseases.[2,3,7,10] However, a variety of complications has resulted from this procedure including papillary damage,[13] perforation of the common bile and pancreatic ducts,[4,6] cholangitis,[2,10] infection of pseudocyst,[7] septicemia and submucosal injection of contrast media.[5] These complications have been relatively rare, and the most commonly reported sequela of retrograde cholangiography and/or pancreatography has been an increase in the serum amylase. The reported incidence of hyperamylasemia has varied from 25 to 61%.[7,8,10,11] Although the incidence of clinical pancreatitis has been relatively rare, fatal pancreatic necrosis may result.[1] The correlation between transient or even lack of elevation in serum amylase, and anatomical, but not necessarily clinical, pancreatitis, is not known. This report presents two patients with focal asymptomatic pancreatitis following attempted retrograde cannulation of the ampulla of Vater which presumably produced a mass involving the head of the pancreas.

From the Departments of Surgery, Medicine, and Pathology,
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Boston, Massachusetts

Case Reports

N.B. (BIH #32-48-17), a 71-year-old woman, was admitted to the hospital with a three week history of jaundice, pruritus and weight loss. She had no known exposure to hepatitis or drugs other than Aldactazide. Although she had no history of pain, she was known to have gall stones for at least three years as demonstrated by oral cholecystography. The patient appeared to be chronically ill and jaundiced. Serum bilirubin was 5.5 mg.%, alkaline phosphatase 289 international units, SGOT 46 international units, amylase 62 units. Retrograde cannulation of the presumed ampulla of Vater was attempted, but the ductal system was not visualized despite the impression of the endoscopist that the tip of the cannula lay within the ampulla at the time of injection. The following day the serum amylase rose to 229 units. Two days following endoscopy, an exploratory laparotomy was performed. The head of the pancreas contained a focal mass with no evidence of fat necrosis or surrounding edema. A cystic duct cholangiogram showed no evidence of a stone within the common duct. A pancreatoduodenectomy was performed for a clinical diagnosis of carcinoma of the head of the pancreas. Microscopic sections revealed acute interstitial pancreatitis limited to the head of the pancreas. The greatest amount of reaction was seen surrounding the pancreatic duct. The common bile duct was noted to enter the duodenum several centimeters proximal to the duct of Wirsung with normal pancreatic parenchyma surrounding it. Liver biopsy demonstrated centrilobular bile stasis consistent with cholestatic jaundice secondary to Aldactazide.

C.B. (BIH #52-66-56), a 64-year-old woman, was admitted to the hospital with a two month history of right upper quadrant abdominal pain, pruritus, jaundice, anorexia and a 10 pound weight loss. Several years prior to admission she had a cholecystectomy. She has no known exposure to drugs other than penicillin. Pertinent physical findings were jaundice and and multiple excoriations. Her liver function studies (bilirubin 13.2, alkaline phosphatase 178, SGOT 41, and SGPT 39) did not change significantly over a two week interval. Retrograde cannulation of the ampulla of Vater was attempted. At various times when it was thought that the catheter was in place, dye was injected, but no radiographic visualization of bile or pancreatic ducts occurred. Patient's serum amylase was normal before and after the unsuccessful

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procedure, and her serum bilirubin did not change. Operation was performed five days later. A 3 × 3 cm firm localized mass with surrounding mild edema was found in the head of the pancreas. The initial impression was that this might represent carcinoma of the pancreas. However, dissection of the distal common duct revealed it to be collapsed. An operative cholangiogram demonstrated obstruction at the junction of both common hepatic ducts and a normal common duct with free flow into the duodenum distally. Biopsy of the bifurcation of the hepatic duct showed primary adenocarcinoma.

Discussion

Retrograde cannulation of the common bile and pancreatic ducts is currently a widely available procedure, but the experience of successful cannulation of the desired duct varies considerably, ranging from 56 to 92% in reported series.[8,9,11,12] Successful cannulation of the common bile duct represents an obvious advance in the differential diagnosis of obstructive jaundice and avoids potential problems associated with percutaneous transhepatic or transvenous hepatic cholangiography. The present report describes two cases presenting a further diagnostic dilemma as a result of attempted retrograde cannulation of the biliary tract. Although successful cannulation in either case was not obtained, manipulations around the ampulla presumably were such as to produce focal inflammatory reaction in the head of the pancreas. Neither patient had symptoms nor signs consistent with a clinical diagnosis of pancreatitis, even though one patient had histologic confirmation of and the other had strong presumptive evidence for the diagnosis. This importance of focal pancreatitis occurring after retrograde cannulation is that it may be grossly indistinguishable from carcinoma of the head of the pancreas.

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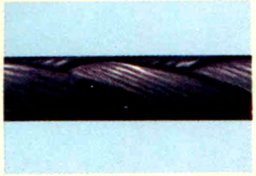

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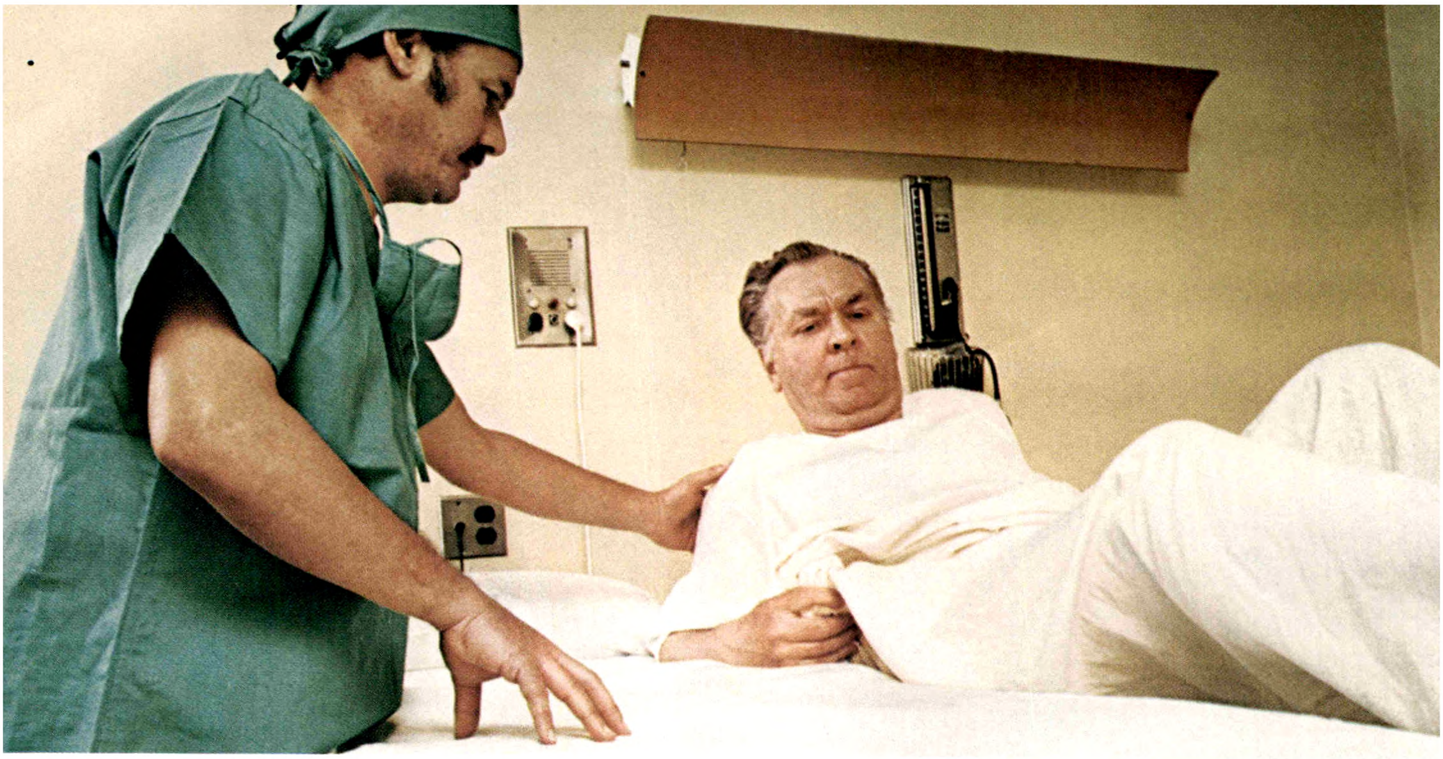

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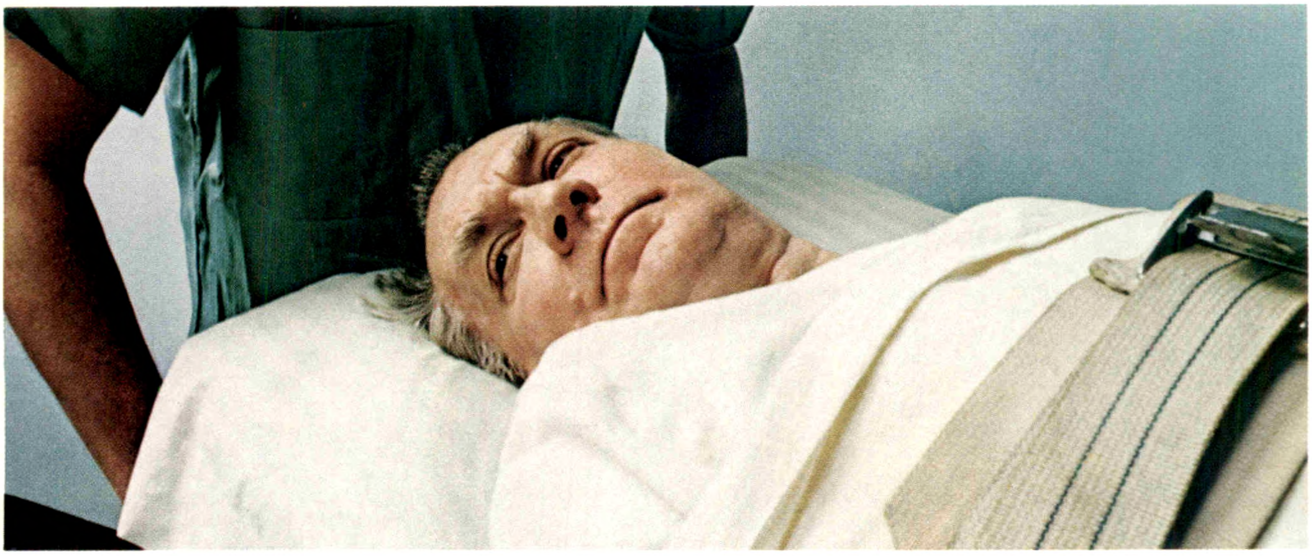

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I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., *dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Moderate psychoneurotic reactions, 2 to 5 mg I.M. or I.V. and severe psychoneurotic reactions, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary; muscle spasm, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); status epilepticus, severe recurrent convulsive seizures, 5 to 10 mg I.M. or I.V. initially, repeat in 2 to 4 hours if necessary. In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V., within 5 to 10 min. prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

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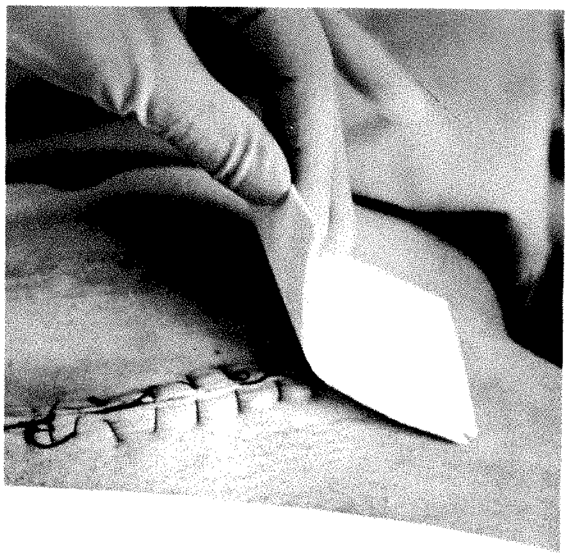

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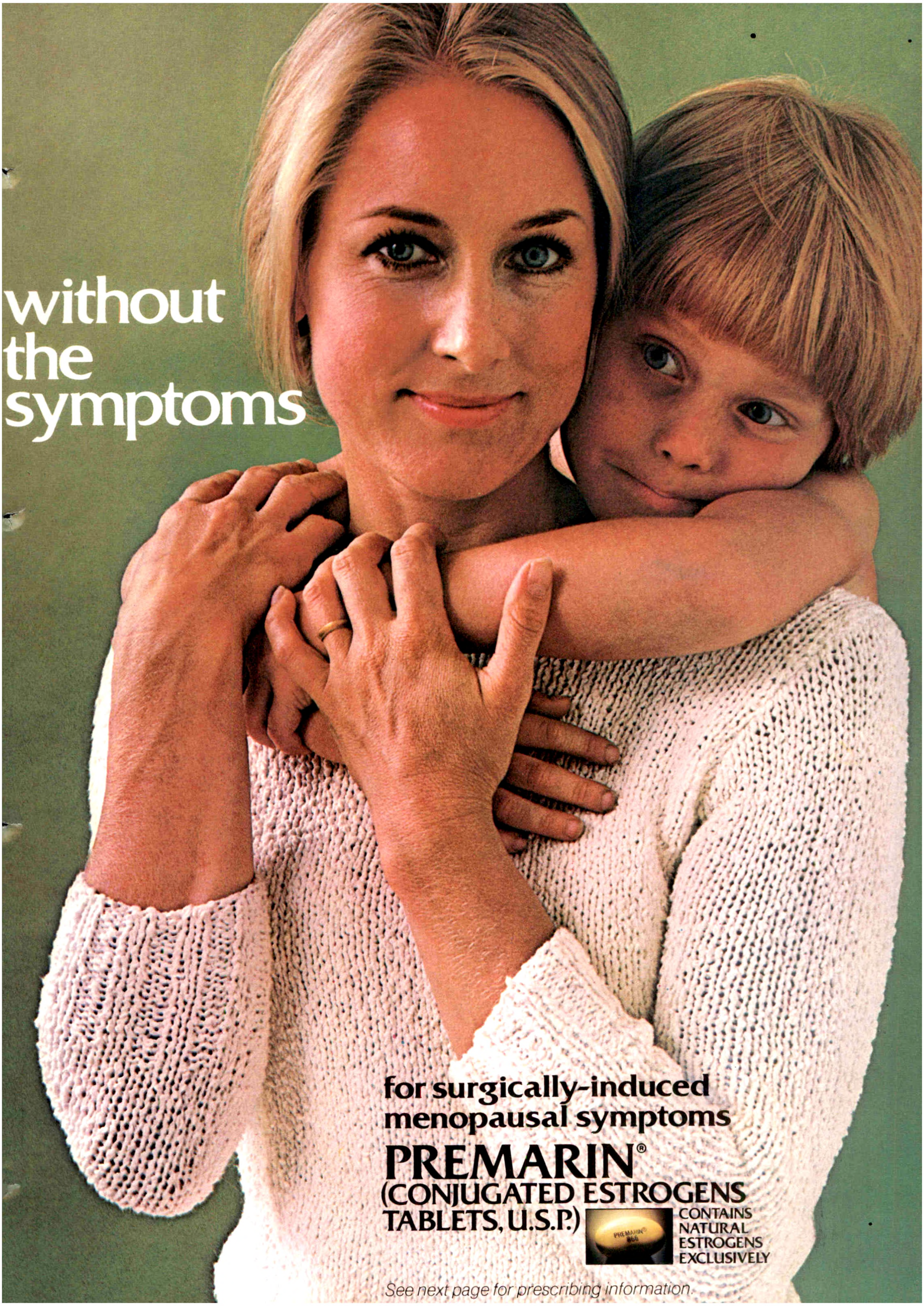
*Conjugated Estrogens Tablets have been evaluated as "probably" effective for postmenopausal osteoporosis.
See prescribing information on last page.


without the symptoms
for surgically-induced menopausal symptoms
PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)
PREMARIN®
866
CONTAINS NATURAL ESTROGENS EXCLUSIVELY
See next page for prescribing information.

BRIEF SUMMARY

(For full prescribing information, see package circular.)

PREMARIN®

(Conjugated Estrogens Tablets, U.S.P.)

Actions: Estrogens are responsible for development and maintenance of the female reproductive system and secondary sex characteristics. They cause the growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for pubertal growth spurt and termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Estrogens are also involved in psychologic and emotional aspects of feminine behavior. As estrogen levels increase during the menstrual cycle, there is a sense of vigor and well-being, and in the menopausal period estrogens aid in relieving nervous symptoms (*e.g.* anxiety, depression and irritability) due to estrogen deficiency. Decline of estrogenic activity at the end of the menstrual cycle can bring on menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the pre- or non-ovulatory cycle, estrogen is the primary determinant in the onset of menstruation. Estrogens do not induce ovulation.

Estrogens affect calcium and phosphorus metabolism, and are involved in maintenance of normal bone structure. In prolonged estrogen deficiency states, administration of estrogen acts to prevent associated bone degenerative changes.

Estrogens appear to be responsible for the relatively greater amount of alpha-lipoprotein and correspondingly lower amount of beta-lipoprotein found in premenopausal women as compared with men.

Estrogens affect the release of pituitary gonadotropins and may also deplete the gonadotropic content of the pituitary.

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.

Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.

Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Estrogen usage may cause preexisting fibromyomata to increase in size; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.

Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:

nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest

Dosage and Administration: PREMARIN should be administered cyclically (3 weeks of daily estrogen and 1 week off) for all indications except selected cases of carcinoma and prevention of postpartum breast engorgement.

Menopausal Syndrome—1.25 mg. daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg. to 1.25 mg. or more daily, depending upon the tissue response of the individual patient. Administer cyclically.

How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)

No. 865—Each *purple* tablet contains 2.5 mg., in bottles of 100 and 1,000.
No. 866—Each *yellow* tablet contains 1.25 mg., in bottles of 100 and 1,000. Also in unit dose package of 100.
No. 867—Each *red* tablet contains 0.625 mg., in bottles of 100 and 1,000. Also in unit dose package of 100.
No. 868—Each *green* tablet contains 0.3 mg., in bottles of 100 and 1,000.

7529

Estrogen replacement when it's needed most

BRAND OF **PREMARIN®**

CONJUGATED ESTROGENS TABLETS, U.S.P.

contains natural estrogens exclusively

Ayerst

AYERST LABORATORIES
New York, N.Y. 10017

T-480
10 ml. Multiple Dose Vial
Talwin®
brand of pentazocine (as lactate)
30 mg. base in 1 ml.
Winthrop
(30 mg. base)
Talwin®
brand of
The alternative to opiates.

Injectable
Talwin®
Brand of
pentazocine
(as lactate)
ampuls of
30 mg. 45 mg. 60 mg.

Winthrop

See important product information concerning adverse reactions, patient selection, and prescribing and precautionary recommendations on reverse side.

Talwin®
Brand of **pentazocine** (as lactate)
Analgesic for Parenteral Use

Ampuls: 30 mg. (1 ml.), 45 mg. (1½ ml.), and 60 mg. (2 ml.)
Vials: (10 ml.) 30 mg./ml.
30 mg. for I.V., I.M., or S.C. use
45 mg. for I.M. or S.C. use
60 mg. for I.M. or S.C. use

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided. In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain. Just as with all medication, the oral form of Talwin is preferable for chronic administration.*

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. As with all strong analgesics, Talwin should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Tissue Damage at Injection Sites. Severe sclerosis of the skin, subcutaneous tissues, and underlying muscle have occurred at the injection sites of patients who have received multiple doses of pentazocine, as lactate. Constant rotation of injection sites is, therefore, recommended. In addition, animal studies have suggested that Talwin may be tolerated less well subcutaneously than intramuscularly.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Dermatologic Reactions. Soft tissue induration, nodules, and cutaneous depression can occur at injection sites. Ulceration (sloughing) and severe sclerosis of the skin and subcutaneous tissues (and, rarely, underlying muscle) have been reported after multiple doses.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia; *other:* tachycardia, weakness or faintness, chills, allergic reactions including angioedema, edema of the face, vascular purpura, toxic epidermal necrolysis.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. When frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: *Uni-Amp®—Individual unit dose ampuls of 1 ml. (30 mg.) and 2 ml. (60 mg.)* in boxes of 25.

Ampuls of 1 ml. (30 mg.) in (nested) boxes of 25.

Ampuls of 1½ ml. (45 mg.) in boxes of 10 and 100.

Ampuls of 2 ml. (60 mg.) in (nested) boxes of 25.

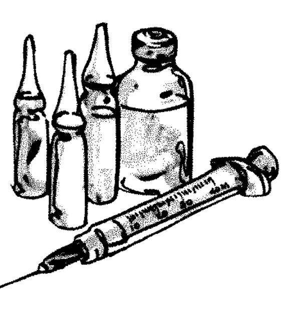
Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

Winthrop Laboratories, New York, N.Y. 10016

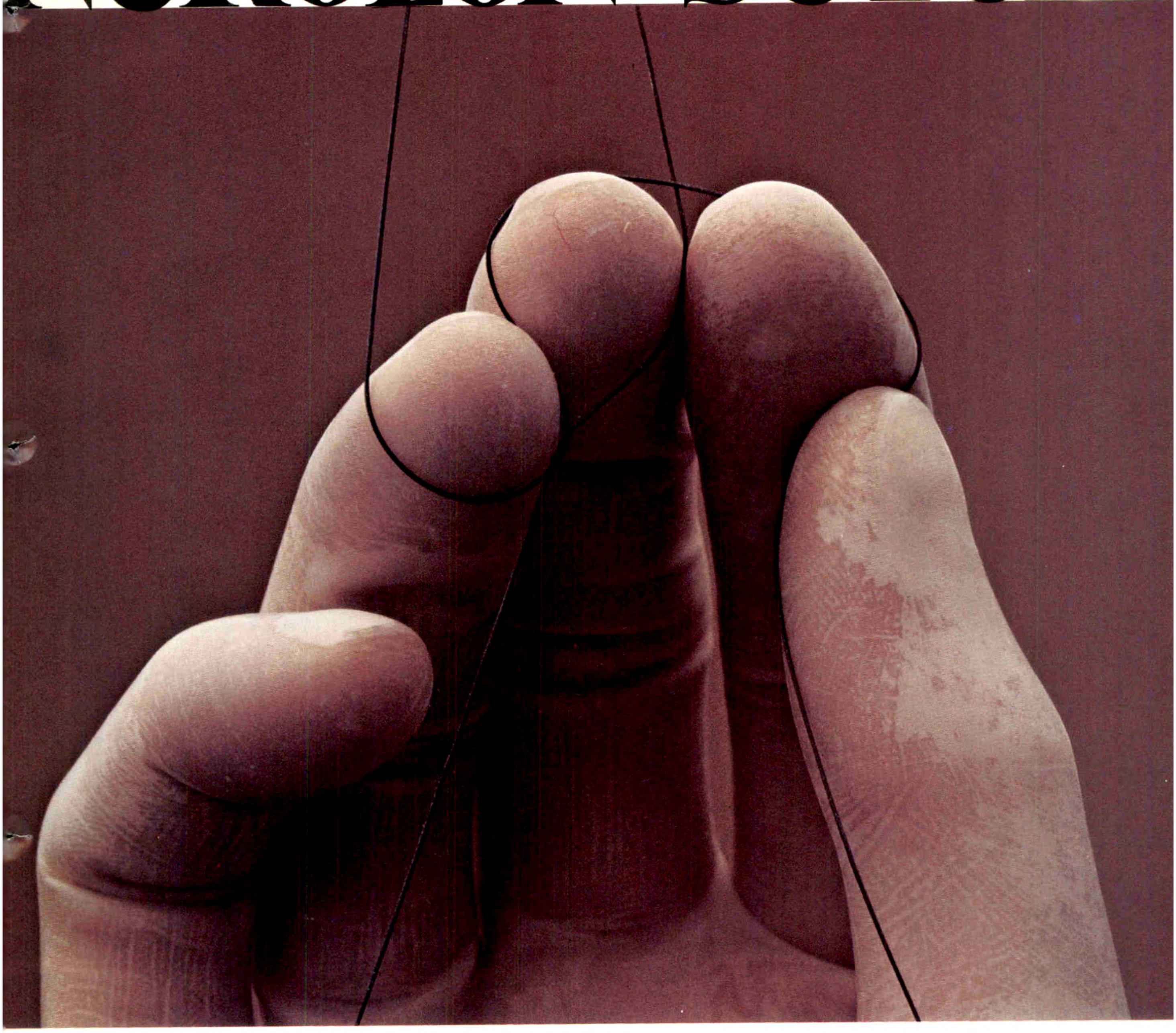
Winthrop
(1660M)



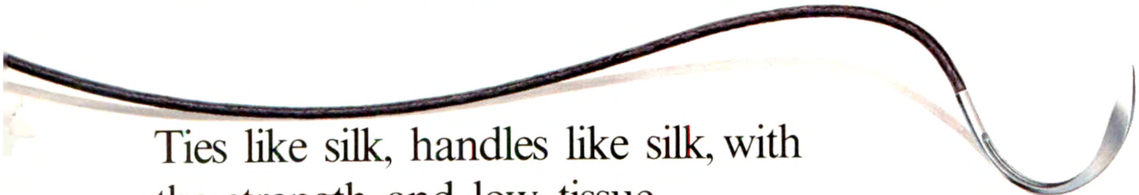
The alternative to opiates.

Injectable Talwin® Brand of pentazocine (as lactate)

NUROLON* SUTURE



The fine handling qualities of silk
are in your hands with
NUROLON Black Braided Nylon Suture.



Ties like silk, handles like silk, with
the strength and low tissue
reactivity of a synthetic.

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Cut out for Forest Hills

Re-live 60 years of action, excitement and great championships in this lavishly illustrated history of the club – and the tournament. With more than 150 photographs, cartoons and illustrations, many in full color. Roll of champions, index, beautiful 8½" x 11½" gift format. At your bookstore or mail coupon today to J. B. LIPPINCOTT COMPANY, P.O. Box 7777-R0400, Philadelphia, Pa. 19175

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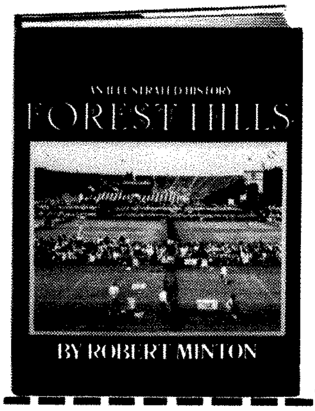

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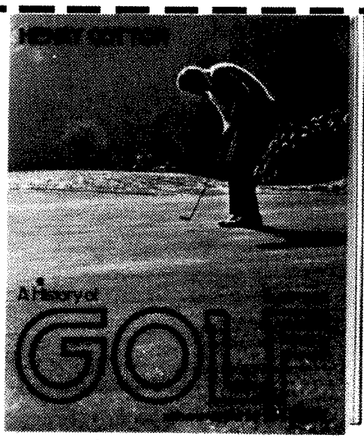

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Follow the world's best players, from "Old" Tom Morris to young Johnny Miller, in this lavish new history by all-time great pro, Henry Cotton. With complete statistics on every major tournament, and more than 150 action photographs – including 30 in full color. "Beautifully illustrated . . . invaluable advice and knowledge."–Sam Snead. At your bookstore or mail the coupon today to J. B. LIPPINCOTT COMPANY, P.O. Box 7777-R0400, Philadelphia, Pa. 19175

Send me_____copy(ies) of HISTORY OF GOLF. I enclose $16.95 each plus 75¢ for shipping. 10-day return privilege.

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DARVOCET-N® 100

propoxyphene napsylate with acetaminophen

Indication: For the relief of mild to moderate pain, either alone or accompanied by fever.

Contraindications: Hypersensitivity to propoxyphene or to acetaminophen.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions. [011375]

DARVON® COMPOUND-65

propoxyphene hydrochloride, aspirin, phenacetin, and caffeine

Indication: For the relief of mild to moderate pain.

Contraindication: Hypersensitivity to propoxyphene, aspirin, phenacetin, or caffeine.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine.

The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Phenacetin has been reported to damage the kidneys when taken in large amounts for a long time.

Salicylates may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions. [011375]

Lilly

Additional information available to the profession on request.

Eli Lilly and Company, Inc.
Indianapolis, Indiana 46206

600390

Relief from her postsurgical pain

Darvocet-N® 100

100 mg. propoxyphene napsylate and
650 mg. acetaminophen

contains no aspirin

**Darvon®
Compound-65**

65 mg. propoxyphene hydrochloride, 227 mg. aspirin,
162 mg. phenacetin, and 32.4 mg. caffeine

contains aspirin

for mild to
moderate pain

See summary of prescribing information on adjoining page.

The open chest.

Another opening for staph[*]?

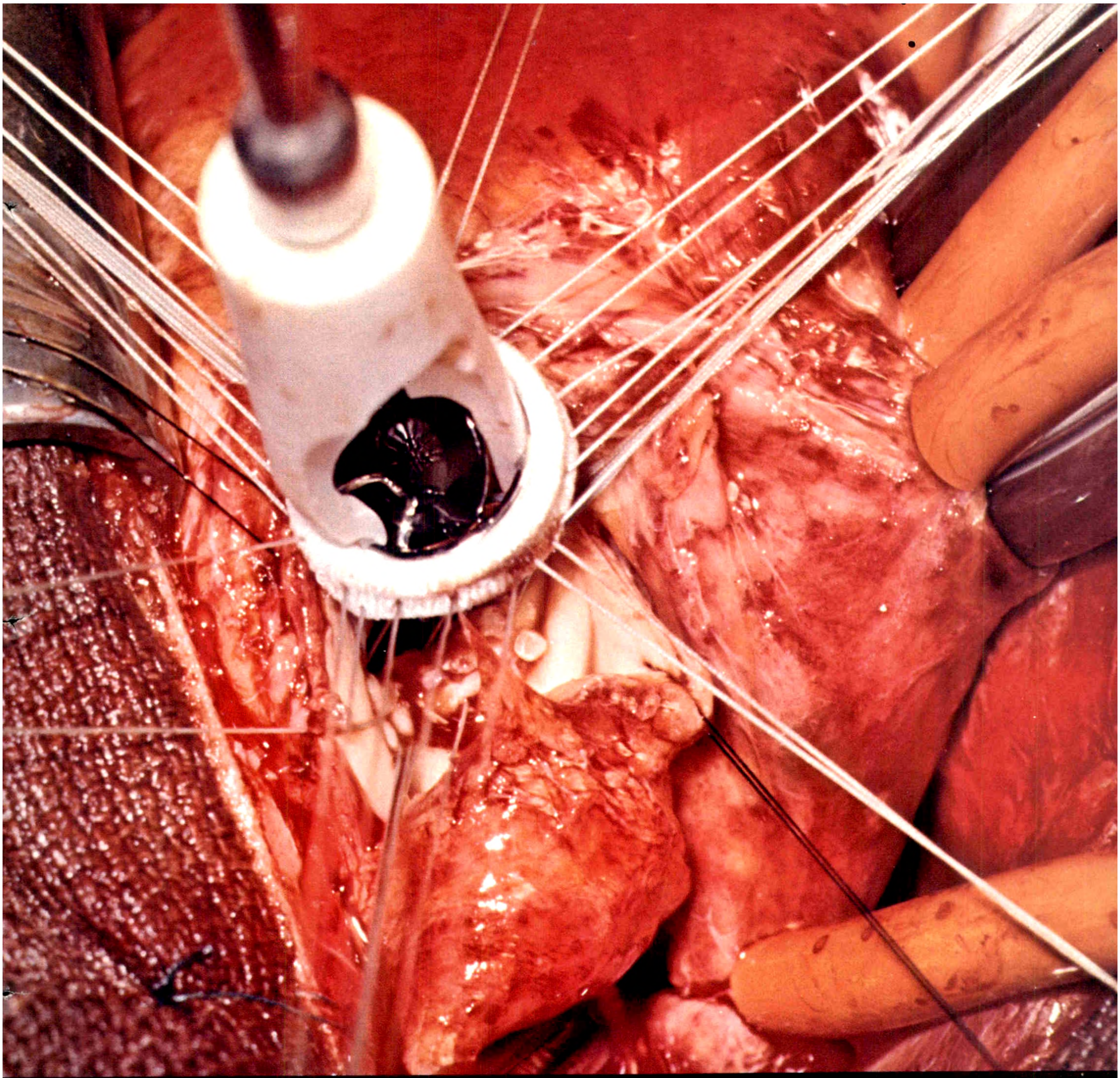
Postoperative surgical infections
Valve replacement: a procedure that can at once sustain life *and* predispose to infection. Although identification of the infectious organism may be difficult, a delay in treatment could result in invasion of the endocardium. The implicated organism may be a penicillinase-producing staph. Progression can be swift and devastating.

Initial antistaph therapy: injection
It's vitally important that effective treatment of bacterial invasion begin as soon as possible. If you suspect the presence of staph and must begin therapy before definitive culture results are known, Injection Unipen® (sodium nafcillin)[†] is a particularly suitable agent.

Appropriate specimens for bacteriologic studies to determine the causative organisms and their susceptibility to nafcillin should be taken prior to the first dose of antibiotic.[†]

Rapid penetration
Unipen appears rapidly in plasma following intramuscular administration. Penetrates body tissues in high concentrations and diffuses well into pleural, pericardial and synovial fluids.

"On call" capability
Reconstitutes in less than 60 seconds. Remains stable for 24 hours.[‡]



Follow-up therapy: oral
Unipen (sodium nafcillin) is available in tablets, capsules, and oral solution as well as the parenteral form. The injectable form should be used initially in severe infections. And as soon as the clinical condition warrants, oral forms of Unipen allow you to continue antistaph therapy with the same antibiotic in a form more convenient to patients.

INJECTION AND ORAL
UNIPEN®
(sodium nafcillin)
as the monohydrate, buffered

Wyeth Laboratories
Philadelphia, Pa. 19101

See important information on next page. ▶

*Nafcillin-susceptible penicillinase-producing staphylococci.
†See Important Note on next page.
‡See important information under Parenteral Administration on next page.

Affords a specific approach to susceptible penicillinase-producing staph infections.

Unipen®

(sodium nafcillin)

AS THE MONOHYDRATE, BUFFERED, WYETH

Ease of reconstitution plus 24-hour stability in I.V. solutions put this potent antistaph agent "on call."
No precipitation, less than 10% loss in activity in I.V. solutions held at room temperature for 24 hours.†

- **5% dextrose in water**
- **5% dextrose in 0.4% NaCl solution**
- **Isotonic NaCl**
- **Ringer's solution**
- **M/6 sodium lactate solution (conc. of 30 mg/ml)**

†See "Intravenous Route" section of Brief Summary on this page.

Indications

The principal indication for sodium nafcillin is in the treatment of infections known to be due to penicillinase-producing staphylococci which have been shown to be sensitive to it.

Bacteriologic studies to determine the causative organisms and their sensitivity to sodium nafcillin should be performed.

If antibiotic therapy is considered necessary in potentially serious infections while awaiting reports of cultures and sensitivity studies, sodium nafcillin may be used to initiate therapy in such patients in whom a penicillinase-producing staphylococcus is suspected (see Important Note below).

In serious, life-threatening infections, oral preparations of the penicillinase-resistant penicillins should not be relied on for initial therapy.

Important Note

When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of sodium nafcillin should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to sodium nafcillin, the physician is advised to continue therapy with a drug other than sodium nafcillin or any other penicillinase-resistant semi-synthetic penicillin.

Methicillin is a compound that acts through a mechanism similar to that of sodium nafcillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in **in vitro** sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

Routine methods of antibiotic sensitivity testing may fail to detect strains of organisms resistant to the penicillinase-resistant penicillins. For this reason, the use of large inocula and 48-hour incubation periods may be needed to obtain accurate sensitivity studies with these antibiotics.

Contraindications

A history of allergic reaction to any of the penicillins is a contraindication.

Warnings

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, appropriate therapy should be instituted, and discontinuation of nafcillin therapy considered. The usual agents (antihistamines, pressor amines, corticosteroids) should be readily available.

Precautions

As with any potent drug, periodic assessment of organ system function, including renal, hepatic and hematopoietic, should be made during prolonged therapy.

The possibility of bacterial and fungal overgrowth should be kept in mind during long-term therapy. If overgrowth of resistant organisms occurs, appropriate measures should be taken.

The oral route of administration should not be relied upon in patients with severe illness, or with nausea, vomiting, gastric dilatation, cardiospasm or intestinal hypermotility.

Safety for use in pregnancy has not been established.

Particular care should be taken with intravenous administration because of the possibility of thrombophlebitis.

Adverse Reactions

Reactions to sodium nafcillin have been infrequent and mild in nature. As with other penicillins, the possibility of an anaphylactic reaction or serum sickness-like reactions should be considered. A careful history should be taken. Patients with histories of hay fever, asthma, urticaria, or previous sensitivity to penicillin are more likely to react adversely.

The few reactions associated with the intramuscular use of sodium nafcillin have been skin rash, pruritus, and possible drug fever. As with other penicillins, reactions from oral use of the drug have included nausea, vomiting, diarrhea, urticaria, and pruritus.

Parenteral Administration

It is recommended that parenteral therapy be used initially in severe infections. The patient should be placed on oral therapy with this product as soon as the clinical condition warrants. **†Intravenous Route:** If given by intravenous infusion, use only these solutions—isotonic NaCl, 5% dextrose in water, 5% dextrose in 0.4% NaCl solution, Ringer's solution or M/6 sodium lactate solution (conc. of 30 mg/ml). Discard any unused portions of I.V. solutions after 24 hours. The concentration of the antibiotic should fall within the range of 2 to 30 mg/ml. The drug concentrate and the rate and volume of the infusion should be adjusted so that the total dose of nafcillin is administered before the drug loses its stability in the solution in use.

There is no clinical experience available on the use of this agent in neonates or infants for this route of administration.

This route of administration should be used for relatively short-term therapy (24-48 hours) because of the occasional occurrence of thrombophlebitis, particularly in elderly patients.

Intramuscular route: After reconstitution, keep under refrigeration and use within 48 hours. The clear solution should be administered by deep intragluteal injection immediately after reconstitution.

Oral Administration

Beta-hemolytic streptococcal infections should be treated for at least 10 days to prevent development of acute rheumatic fever or glomerulonephritis.

If oral therapy is inadequate, resort to parenteral sodium nafcillin.

After mixing, the oral solution must be stored in a refrigerator. Discard any unused portion after one week.

Supplied

INJECTION—Vials of 500 mg., 1 and 2 Gm. Each cc. after reconstitution contains 250 mg. nafcillin buffered with 10 mg. sodium citrate. Film-coated TABLETS—containing sodium nafcillin as the monohydrate, equivalent to 500 mg. nafcillin buffered with calcium carbonate. CAPSULES—containing sodium nafcillin, as the monohydrate, equivalent to 250 mg. nafcillin buffered with calcium carbonate. FOR ORAL SOLUTION—Combination pkg. of vial of dry sodium nafcillin as monohydrate and bottle of diluent—provides 80 cc. of solution containing equivalent of 250 mg. nafcillin per 5 cc. Alcohol 2%.

WYETH LABORATORIES PHILADELPHIA, PA.

Microaggregate Formation in Stored Human Packed Cells:

Comparison with Formation in Stored Whole Blood and a Method for their Removal

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Experiments were performed to compare the formation of microaggregates in stored human whole blood (WB) with that in stored packed cells (PC) and also to compare the effectiveness of standard blood transfusion filters with dacron wool (Swank) micropore transfusion filters in removing such microaggregates. After 5, 10, 15 and 20 days of storage SFP and debris weights of PC's were considerably greater than those of matched WB samples. Passage of either WB or PC's through standard blood transfusion filters resulted in small decreases in SFP and debris weights. Passage of either WB or PC's through dacron wool (Swank) transfusion filters led to striking and highly significant decreases in both SFP and debris weights. When stored PC's were diluted to the same hematocrits as their corresponding WB samples, SFP remained considerably elevated above those of the WB samples. On the basis of this research, it is concluded that centrifugation of blood during component separation leads to a significant increase in microaggregate formation over and above that which progressively occurs during storage and that the risk of pulmonary microembolization during transfusion with stored PC's is greater than that during WB transfusion. For this reason, dacron wool (Swank) filters should always be used when PC's are being transfused.

MICROAGGREGATES consisting mainly of platelets and white blood cells in a fibrin matrix form in progressively increasing numbers as the age of stored human whole blood increases.[1,5–9,12,14,15,19,21] Transfusion of microaggregate-containing blood through standard blood transfusion filters may be a cause for the development of pulmonary insufficiency.[3,5,9,11,14,16,17]

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Even though specific blood components are used extensively in modern surgical practice, the occurrence of microaggregates in stored packed cells has not previously been reported. It was the purpose of this research to compare the formation of microaggregates in human whole blood (WB) with that in human packed cells (PC) prepared and stored under standard blood bank conditions. The effectiveness of standard blood transfusion filters and dacron wool (Swank) micropore blood transfusion filters in removal of microaggregates from stored PC was also compared.

Materials and Methods

Blood from 48 donors which was unacceptable for human use was included in this study (Table 1). None of the donors was receiving medications which are known to cause alterations in platelet adhesiveness. Donors included 42 males and 6 females, and their ages ranged from 19 to 64 years (average age 32.1 years).

Under sterile conditions, one unit (approximately 500 cc) of blood was withdrawn from an antecubital vein of each donor into the collection bag of a plastic triple pack blood storage bag (Fenwal triple pack #HF82P4) containing CPD anticoagulant. Duration of the phlebotomies ranged from 5 to 22 minutes (average 10.1 minutes). Sterile collection methods standard to this center were used.

Each unit of blood was then separated into two equal portions using the two other plastic bags of the triple

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TABLE 1. *Reasons for Rejection of Blood from 48 Human Donors*

Reasons	No. of Patients
History of hepatitis or possible hepatitis exposure (all radioimmunoassay negative)	33
Venereal disease	5
Medical drug treatment	4
History of malaria	3
Miscellaneous	3

pack. One of these aliquots was stored as WB. The other was centrifuged at 5,400 × G for 5 minutes in a RC-3 Sorvall refrigerated centrifuge, the technique standard to this center for separating PC and plasma. The plasma was removed aseptically into a plastic plasma pack. The various aliquots of WB, PC and plasma were stored at 4 C. In this way each separate PC and plasma sample could be compared to its corresponding WB sample throughout the study.

The total of 48 aliquots of whole blood together with its corresponding PC and plasma samples was divided equally into four groups of 12 units each. At five day intervals after initial storage (days 5, 10, 15 and 20) one entire group (including WB, PC and plasma) was removed and studied.

The filter screen to be used for determining screen filtration pressure (SFP) of each aliquot was weighed. SFP was then determined on WB, PC and plasma using a separate preweighed screen for each.[7,8,21] The differential between screen weight before SFP measurement and that after SFP measurement was the debris weight of microaggregates removed from equal aliquot portions of either WB or the corresponding specific component of that WB sample.[13] Hematocrit and white blood cell and platelet counts were also determined on each WB and PC sample.

After completion of these measurements, one-half of each aliquot was filtered through a standard blood transfusion filter* and the remaining one-half was passed through a dacron wool (Swank) transfusion filter.† All tests were then repeated after filtration of these samples.

Results

Statistical analysis was performed on the SFP achieved by each of the various donor groups to determine if the causes for rejection of their blood might have led to changes in SFP (Table 1). No such correlations were found, and the range of SFP achieved by the stored blood from these 48 donors was compatible with the range of SFP achieved by stored human WB which was acceptable for transfusion. Neither was there a statistically significant correlation between the SFP achieved in the stored blood and the time length of the donor's phlebotomy.

Average SFP after each storage time interval and in each group was higher for the PC sample than for the corresponding WB sample (Fig. 1). After 5 days of storage, average SFP of the WB was 67 mm Hg and for the corresponding PC, 320 mm Hg ($P < 0.01$). After 10 days of storage, SFP of the WB was 84 mm Hg and for the corresponding PC, 401 mm Hg ($P < 0.005$). When stored for 15 days, SFP of the WB was 106 mm Hg and that of the PC was 348 mm Hg ($P < 0.0125$). After storage for 20 days, SFP of the WB was 284 mm Hg and that of the PC was 573 mm Hg ($P < 0.01$).

Debris weights from the PC samples were also significantly greater than debris weights from the corresponding WB samples ($P < 0.01$) (Fig. 1).

No significant SFP was measured for any of the plasma samples.

Filtration of WB samples through standard blood transfusion filters resulted in slight decreases in SFP after all storage time spans studied; none of these decreases achieved statistical significance (Fig. 2). Debris weights also decreased, and these changes were statistically significant (Table 2). When WB samples were passed through dacron wool (Swank) filters SFP of all stored samples returned to normal (average 4 mm Hg) (Fig. 2). A striking decrease in debris weights of material passing the filters was of very high statistical significance (Table

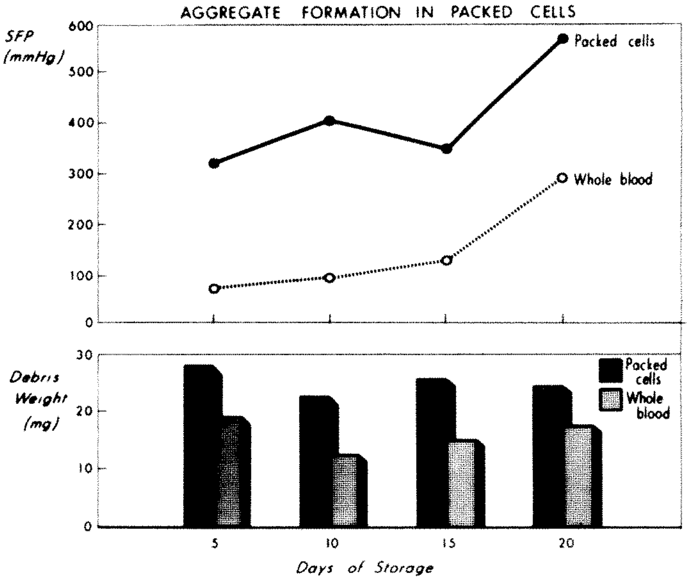

FIG. 1. Screen filtration pressures and debris weights for stored human packed cells were considerably greater than those for matched stored whole blood samples.

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* Cutter "Saftifilter" blood administration set 814–28, Cutter Laboratories, Inc., Berkeley, California 94710.

† Swank transfusion filter, IL-200, Extracorporeal Medical Specialties, Inc., King of Prussia, Pennsylvania 19406.

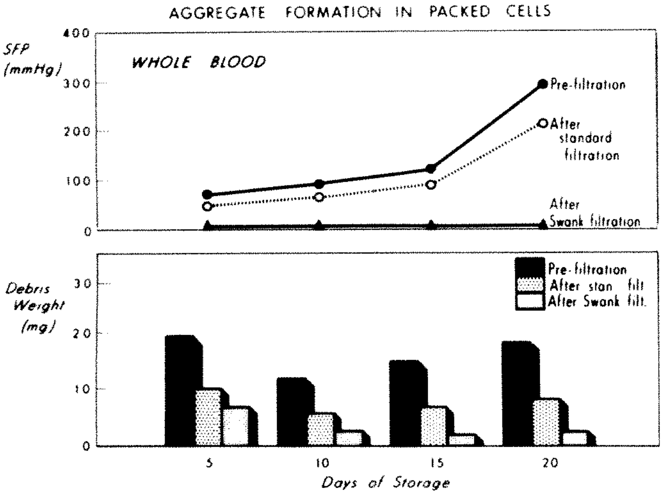

FIG. 2. Passage of stored human whole blood through standard blood transfusion filters caused only slight decreases in screen filtration pressures (SFP) while dacron wool (Swank) filtration returned SFP to normal. In every instance debris weights were greater after passage of the whole blood through standard transfusion filters than after passage through dacron wool (Swank) filters.

2). The differences between the amounts of debris passed by the standard filters and that passed by the dacron wool (Swank) filters were also of high statistical significance (Table 2).

Filtration of PC samples through standard blood transfusion filters led to decreases in SFP and debris weights, none of which were statistically significant (Fig. 3; Table 2). However, decreases in SFP and debris weights after dacron wool (Swank) filtration were of unusually high statistical significance.

After filtration of WB and PC through the standard filters, no statistically significant changes occurred in hematocrits, white blood cell counts or platelet counts. Passage through the dacron wool (Swank) filters caused approximately a 15% reduction in platelet counts at all intervals ($P < 0.0025$).

An aliquot of each of the PC samples was diluted to an hematocrit equal to that of its corresponding WB sample. One-half were diluted with normal saline and the other half with their own stored plasma. SFP of these dilutions were then determined. SFP of samples diluted with saline and those diluted with plasma did not differ. SFP of the diluted PC samples were higher than their corresponding WB samples with the same hematocrits (Fig. 4). These were not of statistical significance after 15 days of storage but after 5, 10 and 20 days, P values were <0.025, <0.05 and <0.05 respectively.

Discussion

Extensive research has verified the progressive accumulation in stored human whole blood (WB) of amorphous aggregates.[1,5–9,12,14,15,18,19,21] These appear to be composed chiefly of white blood cells and platelets with varying amounts of fibrin. SFP is an expression of the number of aggregates in blood, and the weight of aggregates in a unit quantity of blood correlates closely with SFP. As storage time increases, the number and size of the aggregates increase, and SFP of the blood rises.[7,8,12,14,19,21]

In the present research the identical phenomenon was demonstrated to occur in human packed cells (PC) collected and stored under standard blood bank conditions. However, absolute increases in both SFP and debris weights for PC were considerably in excess of those noted in their matched WB samples. These differences can, of course, be partially accounted for simply by the higher cell concentration of the PC. However, other less clear-cut causes must also have contributed to these differences. When PC samples were rediluted to hematocrits corresponding to those of their matched WB samples, SFP of the diluted PC remained significantly higher than those of their corresponding WB samples ($P < 0.05$) (Fig. 4). On the basis of these data it would appear that centrifugation led to a significant increase in microaggregate formation over and above that which would have progressively occurred with increasing length of storage time.

TABLE 2. *Significance Levels of Debris Weights Passed through Transfusion Filters*

	Days of Storage			
	5	10	15	20
1. Whole Blood				
a. Decrease after standard filter	<0.05	NS	<0.01	<0.0025
b. Decrease after Swank filter	<0.005	<0.005	<0.0005	<0.0005
c. Decrease after Swank filter compared to decrease after standard filter	<0.05	<0.01	<0.005	<0.005
2. Packed Cells				
a. Decrease after standard filter	None Significant			
b. Decrease after Swank filter	<0.005	<0.0025	<0.00025	<0.0005
c. Decrease after Swank filter compared to decrease after standard filter	<0.0025	<0.0025	<0.0005	<0.005

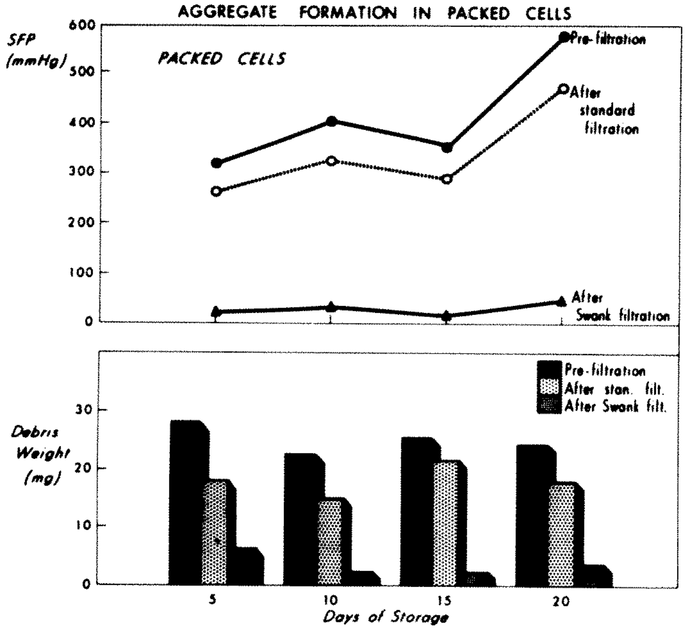

FIG. 3. Passage of stored human packed cells through standard blood transfusion filters caused only slight decreases in screen filtration pressures (SFP); after passage through dacron wool (Swank) filters SFP decreased markedly to an average of 30 mm Hg. Decreases in debris weights after passage through standard filters were not statistically significant, but striking and highly significant decreases resulted after passage through dacron wool (Swank) filters.

Solis has shown that in centrifuged blood there is relative increase in the number of large aggregates and a reduction in the number of small and medium sized aggregates.[19] These particles may be capable of breaking into smaller particles and thus escaping through standard transfusion filters. He proposed this theory as an explanation for the finding of particles up to 56 microns in diameter after filtration of blood through a 40 micron micropore transfusion filter.

A further explanation may also be related to the type of centrifugation used in this study, i.e. 5400 × G for five minutes. This relatively "light" spin may have caused a relative increase in the number of medium sized particles of less than 170 microns in diameter; the escape of these particles through pores of standard transfusion filters would in turn cause an increase in post-filtration SFP of the PC. It may also be that particles causing these changes were not the same ones as those originally formed by the centrifugation, but rather, others that originated *de novo* in the same manner as occurs in stored WB samples. This latter theory is lent some credence by noting that the relative reduction in SFP after standard filtration of 5 day old blood was the same as that noted after filtration of 20 day old blood (16%) even though the absolute reduction in SFP was greater for the 20 day old blood.

In use of the standard "light" spin to separate PC and plasma, the buffy coat is not generally removed from the PC component. Therefore, aggregates, which are composed chiefly of platelets and white blood cells in a fibrin matrix, will remain in the cellular portion, and mixing of this component will result in elevation of SFP. These data confirm that removal of the buffy coat should result in a marked decrease in the number of aggregates in stored PC.

After passage through the dacron wool (Swank) filter, SFP of not only the WB but also the PC returned to normal. Furthermore, the total debris weights from blood samples passed through dacron wool (Swank) filters were almost identical with those removed from matched WB samples which had also been passed through the dacron wool (Swank) filters. This would appear to indicate that the dacron wool (Swank) filter almost completely cleared microaggregates from both PC and WB even though before filtration the concentration of aggregates in PC was considerably higher.

Platelet counts decreased in all blood samples after filtration but achieved statistical significance only following dacron wool (Swank) filtration. Such platelets are not generally considered to be biologically active,[1,4,20,22] and decreased viability and increased adhesiveness may be important factors in their removal by the dacron wool (Swank) filter.

It is beyond the scope of this paper to discuss the contraindications for transfusing to patients blood with an elevated SFP. The danger presented by such transfusions has been discussed elsewhere.[2,3,9,10,12–16] However, on the basis of the present data, it would appear that transfusion of stored PC may place the patient at even greater risk from this hazard than does transfusion of WB. Significantly, greater numbers of microaggregates appear to be present in PC than in an aliquot of WB of the same age containing a similar number of cells. It is also equally

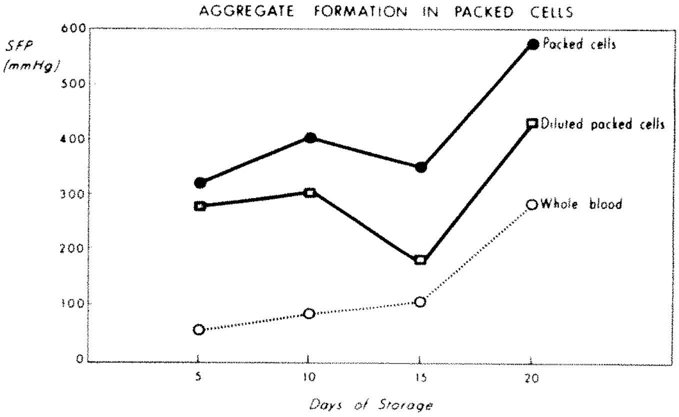

FIG. 4. When stored human packed cells were diluted to the same hematocrits as those of their matched stored whole blood samples, screen filtration pressures remained considerably greater than those of the whole blood samples.

clear that standard blood transfusion filters do not remove most of these microaggregates.

On the basis of previous animal research, it appears that all blood transfusions should be free of microaggregates before such blood is administered to patients. When WB is used, this may be accomplished either by determining prior to transfusion that SFP of the blood is normal or by passing the blood through a dacron wool (Swank) filter during transfusion. In the present research such filters also removed microaggregates from stored PC.

Because of compensatory physiologic mechanisms, administration of one or two units of either WB or PC through a standard blood transfusion filter will probably cause no detrimental changes in a normal human. However, there is no doubt that the risk of pulmonary microembolism is to be avoided when possible, especially in a severely ill or injured patient to whom large quantities of blood must be transfused. Since stored PC's contain more microemboli than does WB, the risk of pulmonary microembolism during transfusion with this component is probably greater than that during transfusion with stored WB of like age. For this reason dacron wool (Swank) filters should be used when PC's are transfused.

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Mesocaval "H" Graft Using Autogenous Vein Graft

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A group of 22 patients with bleeding esophageal varices were treated by creating mesocaval "H" shunts using autogenous veins as the "H" graft. The right external iliac vein was selected as the graft because of its appropriate size in diameter and length, its strength and elasticity. Details in operative technique are outlined. The age of our patients ranged from 24 to 75 years (average age 49), 19 patients had preoperative endoscopy, 10 patients received intraarterial pitressin drip to control hemorrhage, and surgery was done within 10 days of admission in 18 patients. There were two postoperative deaths (both patients Childs Class C), and very few postoperative problems. Right leg edema was a temporary and minimal problem. Encephalopathy was a major problem in only three patients, all of whom had poor hepatic reserve preoperatively. There has been no recurrent variceal bleeding in any of these patients. Our previous experimental data in dogs indicated that the long term patency of these shunts could be assured.

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BLEEDING from esophageal varices is the most dramatic and lethal form of gastrointestinal hemorrhage. In the cirrhotic patient, varix rupture is one of the serious complications which is responsible for the high mortality rate of this disease.

Available public health data indicate this is a growing problem. In 1968, there were an estimated 300,000 alcoholics in New York City alone. In that same year, there were documented 3,000 deaths due to cirrhosis of the liver in New York City, many of whom died from massive variceal hemorrhage. The number of deaths due to cirrhosis has doubled in the past 15 years and there is no indication that the magnitude of the problem is diminishing.[3]

Over thirty years ago, the pioneer work of Whipple, Blakemore and many others clearly demonstrated that portal systemic shunts lowered portal pressure, reduced the incidence of variceal bleeding, and prolonged life in this group of patients.[1,2,4,12,23]

At our own institution, Edmunds and West[8,9] compared the five-year survival of shunted and non-shunted patients with bleeding esophageal varices. The patients treated with portal systemic shunts had a survival rate three times that of the non-shunted individually treated group. Other similar studies[4,12] confirmed this basic fact that patient's with bleeding varices survived longer after portal systemic shunts.

Materials and Methods

Experimental Work

Throughout the country, the most popular types of portal decompression are the end-to-side portacaval shunt, or some type of spleno-renal shunt. There are clearly times when such procedures are technically impossible to perform or at best will involve a bloody and tedious struggle. Several years ago we began an experimental study of various types of mesocaval "H" grafts in dogs using composite vein grafts. In all 15 dogs, these shunts were widely patent at sacrifice at 6 weeks (Fig. 1). There was no evidence of kinking, occlusion or thrombosis of the grafts in any of these animals.[15]

Encouraged by this experimental work in dogs, we embarked on treating a series of patients bleeding from esophageal varices. Mesocaval "H" grafts were created using autogenous vein grafts. We have abandoned the use of composite vein grafts because they are tedious and time-consuming to create. The right external iliac vein has been selected, and it represents a very suitable conduit for venous shunting. It seems to be of almost ideal diameter, strength and elasticity for such a shunt, has very few tributaries that need ligation, and is easily obtainable. With the entire peritoneal cavity widely opened, it is relatively easy and safe to dissect out this vessel.

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Operative Technique

The patient is placed in the supine position with ace bandages applied from toes to groin. A central venous catheter is placed and a Foley catheter inserted into the bladder. A long midline incision is made from the xyphoid to the pubic symphysis. Once inside the peritoneum, ascites is measured and exploration carried out with particular attention to the stomach and duodenum, looking for evidence of peptic disease. Liver biopsy is preferably obtained after the shunt.

The omentum and transverse colon are lifted cephalad, and the small bowel is retracted to the left. We often eviscerate the small bowel, placing it in rubber sheeting or towels. The transverse mesocolon is thus exposed and a transverse incision is made at the base of the mesocolon and extended to the left over the mesenteric vessels. This maneuver exposes the third portion of the duodenum, which is mobilized and retracted cephalad and to the left. The inferior vena cava thus exposed is dissected from the adventitia in order to facilitate application of a Satinsky clamp. Several small venous tributaries may require ligation.

The superior mesenteric vein is identified and dissected free; the pulsation of the superior mesenteric artery serves as a useful guide to its location. Dissection must be done with great care as these vessels are fragile; venous collaterals must be divided and an umbilical tape placed around the superior mesenteric vein.

The next step is to dissect out the external iliac vein, which will be used as the "H" graft. Tapes are placed around both artery and vein to facilitate dissection. A segment of vein approximately 7 to 8 cm in length is generally necessary and the vein must be freed from its exit from the peritoneal cavity and dissected cephalad towards the common iliac vein. This vessel must be *doubly ligated in continuity at both proximal and distal ends using suture ligatures*. In one patient, inadequate control of the distal stump necessitated re-exploration for control of hemorrhage. If necessary, the internal iliac vein is sacrificed and doubly ligated to obtain adequate length for the vein graft.

The caval-graft anastomosis is done first. A Satinsky clamp partially occludes the cava and a "window" is excised from the left anterior aspect of the cava. Standard running suture using 5-0 Ethiflex® is employed. The anastomosis is carefully checked for leaks.

The superior mesenteric vein is exposed and a baby Beck vascular clamp is applied to the right lateral aspect of the vein, occluding most of the vessel. The vessel is incised (no window excised) for the length of the diameter of the vein graft. The corner sutures are tied and "stay" sutures are placed to retract the anterior walls of both the superior mesenteric vein and the vein graft (Fig. 2). The posterior walls are approximated, using the intraluminal running suture technique, and the anastomosis completed anteriorly (Fig. 3).

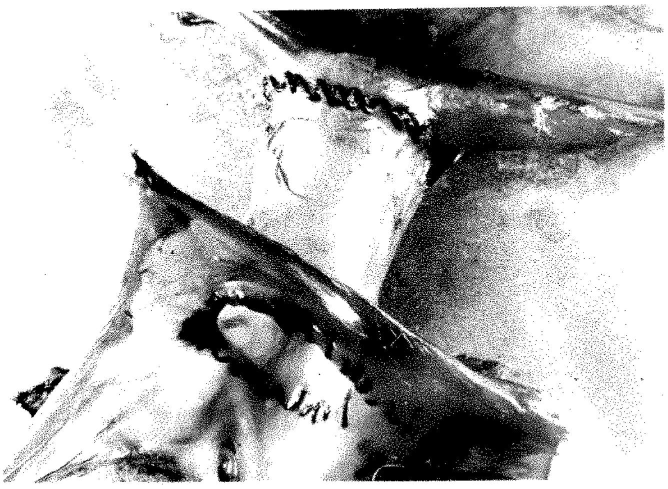


FIG. 1. Autogenous vein mesocaval "H" graft in experimental animal at sacrifice. Note the wide patency of graft without stenosis of anastomosis.

Once the vein graft shunt has been tested and is satisfactorily in place, pressure and flow measurements can be done with the shunt occluded and opened. A liver biopsy is now obtained (Figs. 4 a, b and c).

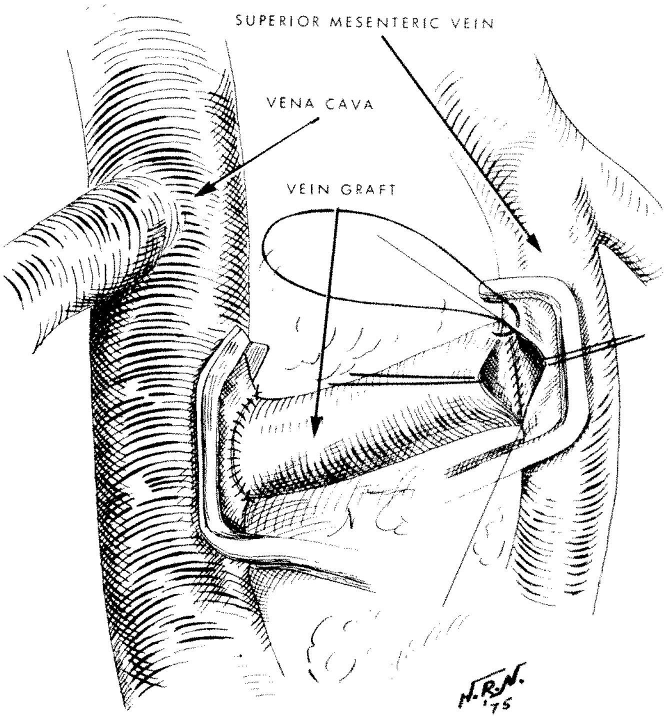


FIG. 2. The autogenous vein graft has been anastomosed to the vena cava first. The graft-mesenteric vein anastomosis is being completed anteriorly. Note the stay sutures retracting the anterior walls of the vessels, making easy exposure for completing the posterior wall anastomosis.

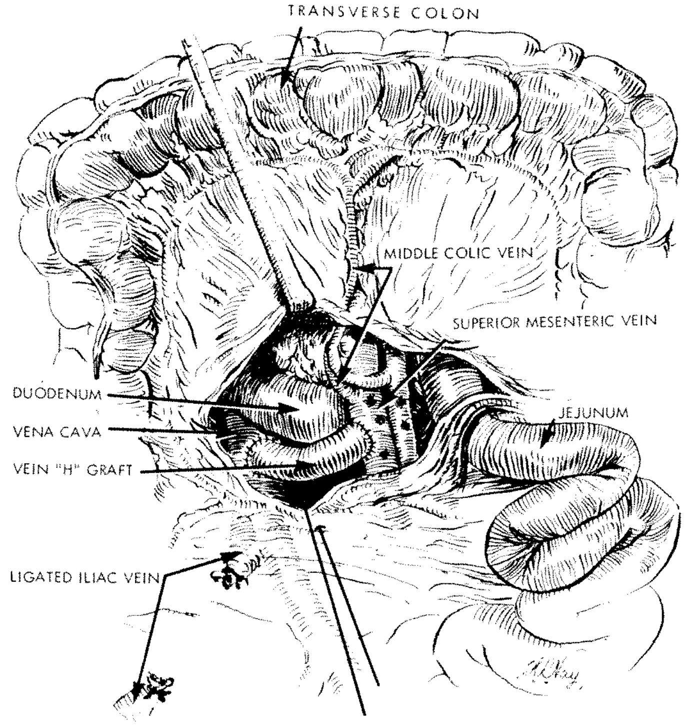


FIG. 3. Mesocaval "H" vein graft in place just caudad to the sweep of the duodenum. Note the transverse incision at the base of the transverse mesocolon that exposes the vena cava, duodenum and superior mesenteric vessels. The doubly ligated ends of the iliac vein are seen as well.

Clinical Approach and Experience

Within the past few years, we have made every effort to have each patient with gastrointestinal bleeding seen by the a surgeon, the gastrointestinal group and an internist. The initial evaluation of each patient is made by the cooperating groups. Blood volume replacement, fluid and electrolyte administration are undertaken quickly. Early endoscopy is most important and preferably done by the most senior and experienced endoscopist. Positive identification of the bleeding site is important. If doubt remains, a repeat endoscopy is performed.

Careful evaluation of liver function studies, clotting factors, encephalopathy, ascites and hypokalemia is carried out and abnormalities are corrected when possible. An early decision is made as to whether the patient is a possible surgical candidate. Recently, we have undertaken shunts on quite sick patients as our criteria have become more lenient than in the past.

If the patient is a possible surgical candidate, and there is evidence of continuing bleeding, intravenous pitressin is given, and a catheter is placed in the superior mesenteric artery under fluoroscopic control for the continuous administration of intra-arterial pitressin. Initially, a flush arteriogram is made to insure that an anomalous hepatic artery does not arise from the superior mesenteric artery. If the anatomy is normal pitressin is infused into the superior mesenteric artery using a sigmomotor pump to keep this flow constant and controlled. Perfusion of pitressin at a rate of 0.3 units/minute in 5% D/W is started. After five minutes a repeat angiogram is done to document decreased flow in the superior mesenteric artery. Then, pitressin is perfused alternately, at a rate of 0.3 units/minute for 20 minutes then at 0.15 units/minute for 20 minutes. The perfusion is kept up from 4 to 48 hours after the bleeding has stopped[5,14].

In the vast majority of our patients bleeding is temporarily controlled using this technique, and we have used this "borrowed time" to correct chemical and metabolic disorders, replacing deficits in albumin, blood volume, to correct ascites and clear encephalopathy when present. Our experience, and that of others, indicates that patients will rebleed once the pitressin drip has been stopped. For this reason surgery is undertaken within the next 24 to 72 hours.

Clinical Series

Twenty-two patients with bleeding esophageal varices have undergone mesocaval "H" vein shunts using autogenous vein grafts at St. Luke's Hospital Center. The underlying etiology of the varices was Lannec's cirrhosis in 19 patients, post necrotic cirrhosis in 2, and in one extrahepatic block (Table 1).

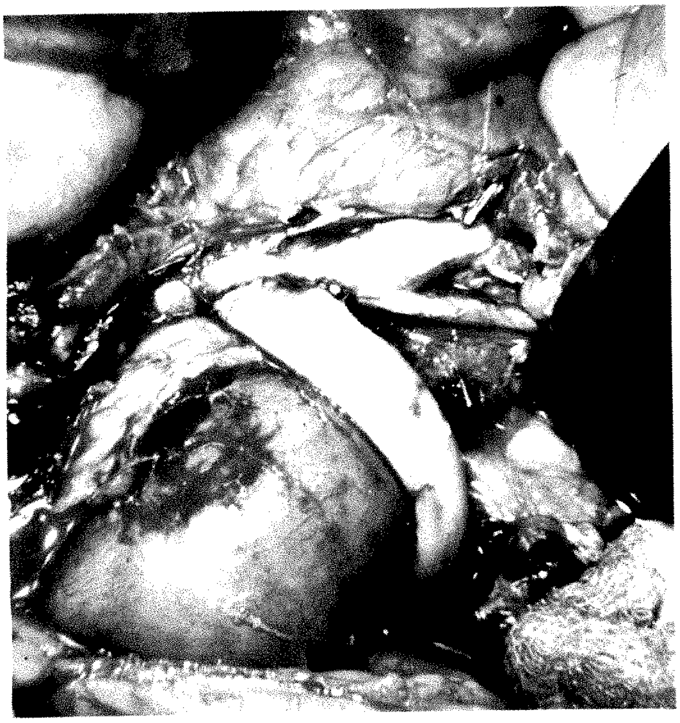
Child's classification of liver function was determined as soon as possible after admission. Of the 22 patients, 6 were classified as A, 9 as B, and 7 as Class C. It is impossible to exactly classify some patients but the data were reviewed as carefully as possible, and our breakdown of patients falls roughly into the above grouping.

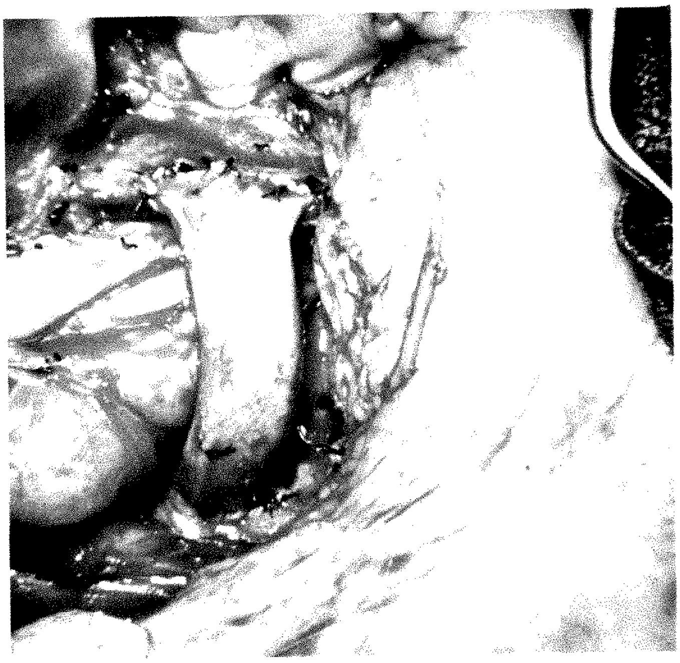
The age of our patients varied widely, the youngest was 25 years old, and the oldest was 75 years old, with an average age of 49 years. Preoperative endoscopy was done on 19 of the 22 patients, the others having had x-ray studies to confirm the diagnosis (Table 2). Several patients were transferred from other hospitals with Blakemore-Sengstaken tubes in place.

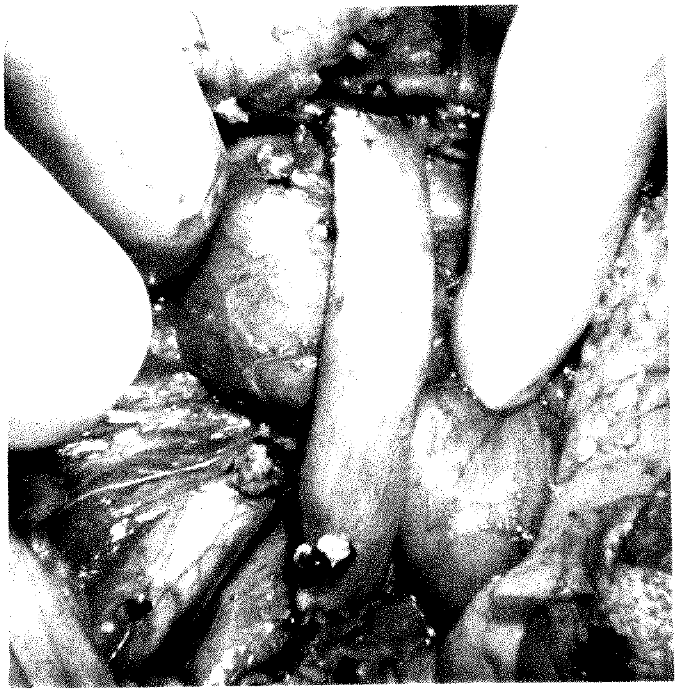
During the preoperative period 10 patients had intra-arterial pitressin drip which controlled their bleeding. This was successful in only 8 patients and the others required esophageal tamponade.

Of our 22 patients, 18 underwent surgery within 10 days of admission. Our aim was to prepare these patients for surgery within 72 hours, having controlled their hemorrhage as well as metabolic abnormalities, ascites and encephalopathy.

During surgery, portal and vena caval pressures were measured before and after shunting. Portal pressures dropped an average of 131 mm saline following completion of the shunt. This drop is not as dramatic as the fall encountered after standard end-to-side portal caval shunts, but we feel it is adequate to prevent recurrent variceal bleeding. The average blood replacement







FIGS. 4 a to c. Complete mesocaval "H" graft bridging the inferior vena cava (superiorly) and the vena cava (inferiorly). Note the adaptability and flexibility of these autogenous grafts affording adequate sized anastomoses without kinking.

during surgery was 650 ml which reflects the relative ease of dissection when compared to blood loss encountered in the standard portacaval shunt (Table 3).

Postoperative complications (Table 4) have been gratifyingly low. There was no recurrent variceal bleeding, although four patients did bleed from gastric ulcers which responded to appropriate medical therapy. We have watched closely for development of leg edema since the external iliac vein is sacrificed. There have been four episodes of temporary calf and thigh edema in the right leg, all of which were treated with elastic support. The edema generally was easily controlled and disappeared completely by 5 weeks. In one patient the edema lasted for 6 months. There has been no late development of edema (Fig. 5).

Some degree of encephalopathy was noted in 6 of our 22 patients and in three it was severe enough to require readmission and treatment. In two of these three patients, the encephalopathy was related to bleeding gastric ulcers. Both of these patients had severely impaired liver function preoperatively (Childs Class C). One patient required a course of Leva Dopa before she responded and her sensorium cleared.* The other three patients responded to protein restricted diets and a course of oral neomycin, and they have returned to good health. We feel, as others do, that encephalopathy is primarily a function of hepatic reserve. When patients with markedly impaired liver function are treated, a certain percentage of patients will develop episodes of encephalopathy. There was no instance of worsened orientation and several patients showed great improvement in their general outlook. These patients often responded dramatically to the ministrations and interest of the physicians caring for them, perhaps reflecting their basically dependent personality. Our feeling is that careful followup and genuine interest in these people is essential if they are to adhere to a non-alcoholic regimen.

There were two deaths in the postoperative period. The first, a 25 year old alcoholic and narcotic addict was

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* Patient last seen January 1976 4½ years post-shunting no ascites, no encephalopathy, and on no medications.

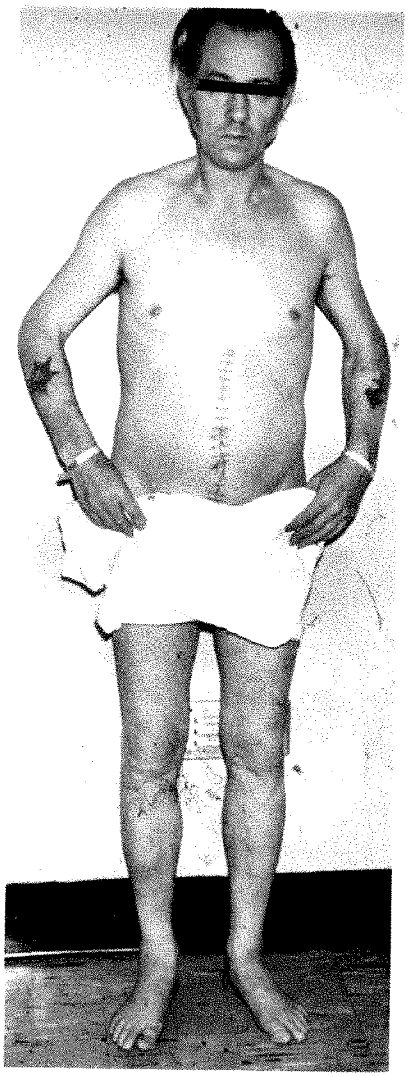

FIG. 5. This patient had undergone a mesocaval "H" graft sacrificing the right external iliac vein 2½ weeks prior to this photograph. Note that no edema of the leg is noted. There has been no permanent leg edema in this series of 22 patients.

considered a Class C candidate. He had severely impaired liver chemistries, ascites, a bleeding diathesis and underwent a mesocaval "H" graft. Severe congestive hypersplenism was present preoperatively, and after shunting diffuse and uncontrolled hemorrhage occurred. He died on the tenth postoperative day. This patient was one of our early cases, and would not have been operated on today using our present criteria. The second patient, also Class C, died of progressive liver failure during the postoperative period. At autopsy the shunts were widely patent in each patient.

TABLE 1. *Mesocaval "H" Grafts (with autogenous vein): 22 patients*

Diagnosis: Proven Bleeding Varices	22 (100%)
Laennec's Cirrhosis	19
Post Necrotic Cirrhosis	2
Extrahepatic portral vein obstruction	1
	22

TABLE 2. *Patient Data*

Age Range	24–75 yrs (avg 49 yrs)
Preop Endoscopy	(19/22) pts
Intra-arterial Pitressin Drip	(10/22) pts
Emergency or Urgent Surgery	(18/22) pts

TABLE 3. *Operative Data*

Portal Hypertension (measured at surgery)	100%
Portal Pressure Drop After Shunt (Avg)	131 mm saline
Blood Replacement (Avg)	650 ml

Discussion

Whipple,[23] Blakemore,[2] Child,[4] Rousselot,[9] Linton and Ellis[12] and many others[22] have clearly demonstrated that portal-systemic shunts lower the pressure found in portal hypertension and reduce the incidence of variceal bleeding. Edmunds and West,[8,9] at our own institution, demonstrated conclusively that the five-year survival in patients with bleeding esophageal varices was impressively greater in the shunted patients when compared to those patients treated medically. When faced with the patient with bleeding varices, the question is not whether a shunt should be done, but rather which kind of shunt and what timing.

The work of Orloff[16] has stimulated us to approach these patients vigorously, and as we have indicated, the majority have been operated upon within ten days after admission. This is a major departure from previous policy and attitudes. Previously, we held very rigid criteria in selecting patients for portacaval shunts, and currently we are operating earlier on sicker patients. We do not agree with Orloff's recommendation that surgery be undertaken within 8 hours of admission. Evaluating and correcting electrolyte derangements, blood volume deficits, hematologic defects and correcting or controlling ascites, all seem important and worthy of efforts to correct before surgery. Our mortality rate of 2 of 22 patients (both deaths occurring in severe cirrhotics) would suggest that this policy has merit.

The need for shunts of adequate calibre has been alluded to by many workers. The special problem of extrahepatic block has made the search for other means of portal decompression a continuing problem.[22] In 1966, we reported our first experience using an autogenous vein "H" graft for portal decompression which led us to our present policies and approach to bleeding varices.[15] Read, et al.[18] presented their experience in 7 patients using mesocaval "H" homografts. Stipa et al.[20] have shown their technique in using autogenous vein "H" grafts obtained from the external jugular vein in 8 patients without operative mortality.

TABLE 4. *Complications*

POSTOPERATIVE COMPLICATIONS	*Temporary*	*Permanent*
Leg Edema	4	0
	Temporary and Controlled	*Severe* (Class C Patients)
Encephalopathy	3	3*
	Peptic Ulceration	*Variceal*
Recurrent GI Bleeding:	4	0
Ascites with dilutional hyponatremia: (present preop)	1*	
Deaths (both Class C Patients):	2	
Liver Failure:	1	
Hypersplenism with bleeding diathesis:	1	

* At followup the patient had no ascites, no encephalopathy and was taking no medications.

Others, including Foster et al.,[11] Preston and Trippel,[17] and more recently Drapanas,[7] have used plastic prostheses as mesocaval "H" grafts with apparent good results and low mortality. We have used this technique in four patients but our preference is for the autogenous vein. The prosthetic tubes are cumbersome to work with, and the tendency to kinking and twisting is great, particularly after the small bowel mesentery is returned to its normal location.

There has been ample research to clearly indicate that autogenous vein grafts provide the most satisfactory material for venous grafting.[21] Dale and Scott[6] reviewed and studied grafts in the venous system and concluded that autogenous vein grafts were the most satisfactory. Escamilla and Ellis[10] performed experimental portacaval "H" shunts with Teflon grafts and found a 50% patency rate.

Lord, et al.[13] used Teflon tubes for mesocaval "H" grafts in a group of 5 patients; there was one death. At autopsy the shunt was thrombosed. They found a thick neointima lining and therefore use an 18 millimeter Teflon prosthesis to allow for the formation of this neointima.

We are convinced that the mesocaval "H" shunt using autogenous vein creates a suitable method of portal decompression in the patient with portal hypertension and bleeding varices. We have not encountered kinking or obliteration of these shunts. The problem of leg edema following sacrifice of the right external iliac vein has been minimal, and in all cases, temporary. Recurrent variceal bleeding has not occurred, although there were 4 patients with bleeding gastric ulcers.

We are currently studying portal blood flow using the electromagnetic flow meter both pre and post shunting, to evaluate more concisely the effects of our mesocaval "H" vein grafts upon the flow through the liver.

The problem of postoperative encephalopathy is frequently discussed in the medical literature, and in our experience is closely related to the preoperative hepatic reserve. When recognized early and treated effectively, encephalopathy has been a serious problem in only 3 of our patients.

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Peripheral Vascular Anastomotic Aneurysms:

A Fifteen-Year Experience

W. GRAHAM KNOX, M.D.

A 15-year experience with anastomotic aneurysms resulting from peripheral vascular reconstruction is presented. The analysis is divided into three 5-year periods. It is obvious from this presentation that the etiology is probably caused by suture material, end-to-side anastomosis, proximity of the anastomosis to a joint and intimectomy of the recipient artery at the original operative procedure. None of the lesions reported herein were associated with graft or wound sepsis. Anastomotic aneurysms at the proximal aortic suture line resulted in aortoenteric fistulae in 6 of 8 cases. There were no survivors in these 6 cases despite successful graft replacement. It is to be emphasized that the complication of anastomotic aneurysm still remains a significant complication in peripheral vascular surgery with a 1.9% incidence noted in 320 operations performed from 1970–1974.

ANASTOMOTIC ANEURYSMS fortunately occur rarely when one considers the number of angioplastic procedures now being performed for peripheral vascular degenerative disease. Although some authors[8,9] have reported an incidence of 20–30% of suture line aneurysms, perusal of the recent literature indicates this complication as becoming progressively less frequent.[1,7] Christiansen *et al.*[3] reported only 7 aneurysms in 1500 grafts anastomosed to the femoral artery in the years 1965–1970. In view of the paucity of reports relating to anastomotic disruptions in the last 5 years it was thought pertinent to emphasize the continuing, though lessened, problem of these lesions by reporting a series of 36 aneurysms occurring in 28 patients seen at St. Luke's Hospital Center and St. Vincent's Hospital and Medical Center in the 15-year period from 1959 to 1974 (Table 1). None of these aneurysms was associated with graft or wound sepsis. Although aneurysms occurring at the aortic suture line presented as aortoenteric fistulae in 6 of 8 instances not one was septic in origin. Followup to the present was obtained for all patients surviving in this series. Six of the 28 patients had their original vascular reconstruction performed in other hospitals.

From the Vascular Service, St. Luke's Hospital Center and St. Vincent's Hospital and Medical Center, New York, N.Y.

Etiology

Causative factors, other than infection, have been well described in the literature.[3,6,7]

In order of importance, suture material, end-to-side anastomoses, proximity to a joint and intimectomy of the recipient artery at the original operation are usually indicted as the principal causes. Graft material and composition, hypertension, postoperative heparinization and perigraft cicatrix with graft retraction are lesser considerations. It is difficult, in analyzing a series of such lesions, to clearly delineate one causative factor in each instance. As shown in Table 2, the number of aneurysms associated with the principal etiological cause are defined. It must be emphasized that in some cases a combination of causes played some role in initiating the suture line disruption. The fact that 29 of these lesions occurred in end-to-side anastomoses and 22 of these were located at the common femoral artery anastomosis in proximity to the hip joint isolates a major cause or combination of causes for anastomotic aneurysm.

As regards suture material used in the primary angioplastic operation, it is demonstrated in Table 2 and 3 that of the series of the 36 anastomotic lesions, silk was employed in 7, monofilament polyethylene sutures in 15 and braided Dacron in 14.

In those patients in whom the original vascular reconstruction had been peformed in 1959–1964 either braided silk or monofilament polyethylene were used in 17 of the

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TABLE 1. *Anastomotic Aneurysms January 1959–January 1974*
36 Aneurysms–28 Patients

Location	No.	Graft Type	
Aortic Anastomosis	8	Knitted Dacron	33
Iliac Artery Suture Line	2	Woven Dacron	2
Femoral Artery Suture Line	22	Woven Teflon	1
Popliteal Artery Suture Line	3		
Dacron-Dacron Suture Line	1		

18 procedures (Table 3). Anastomotic separations were probably directly related to either fragmentation of the synthetic material or phagocytosis of the attenuated silk material as originally described by Cutler and Dunphy.[4] One can note (Table 3) that silk and monofilament synthetic sutures were not used in the last 5 years that this report subtends, but 6 aneurysms have occurred in patients having their primary operation performed in the last 5-year period. This emphasizes that anastomotic aneurysm remains a continuing problem even though the incidence of occurrence has been significantly reduced.

The time interval between the original vascular procedure and the diagnosis of the aneurysm averaged 29 months in this series (Table 4). This concurs with the reports of others with Stoney[9] reporting 25 months and Sawyers *et al.*[7] documenting an average 44 month interval. Those few authors[8] reporting suture line separations occurring within one or two months post-grafting would indict surgical technique as the prime causative factor. The greatest incidence of anastomotic lesions occurred between one and 3 years postoperative (Table 4).

Sixteen of the 28 patients in this series were mildly to moderately hypertensive. No patient operated upon in the reporting hospitals had anticoagulation therapy in the immediate postoperative period. Intimectomy of the recipient artery was performed in 8 patients. It must be emphasized that in no single instance could it be documented that intimectomy per se was the sole cause of the anastomotic disruption, but probably was a contributing factor in these patients.

Diagnosis

It is to be stressed that, with the exception of the aortic suture line aneurysms, the diagnosis of anastomotic aneurysm in this series was obvious at the time of hospital admission. Although angiographic studies were performed on a few patients it was not required in the majority of cases. In the 8 cases of aortic suture line pathology 6 patients had symptoms of aorto-enteric fistula. This, without exception, was heralded by gastrointestinal hemorrhage and has prompted us to treat all patients with retroperitoneal aortic grafts who have gastro-intestinal bleeding by emergency laparotomy, with only the rarest exceptions. Since 7 of our 8 patients with aortic suture anastomotic aneurysms died in the hospital, usually as the result of unnecessary diagnostic delay, we consider such cases as urgent emergencies. It is of interest to record that of the 6 aortic-enteric fistula cases all had ruptured into the duodenum via an aneurysmal defect and not directly from the suture line into the intestinal lumen. This would infer that it is the pressure of an expansile aneurysm against the posterior duodenal wall rather than mere adherence of the bowel to the suture line per se that serves as the initiating factor in the fistulation.

TABLE 2. *Etiology Anastomotic Aneurysms: Non-infected*

Original Operation	No. Aneurysms
Suture Material	
Silk	7
Monofilament Synthetic	15
Braided Synthetic	14
End–end anastomoses (aortic)	7
End–side anastomoses (aortic)	1
Intimectomy host artery	8
End–side anastomoses	28
(Proximity to joint)	22

Symptomatology

With the exception of the retroperitoneal aneurysms, patients with anastomotic rupture complained only of vague pain at the site of the lesion or noted the presence of a pulsatile mass. Regardless of the graft material, suture material or duration of graft patency, no patient with massive hemorrhage as the initial complaint had anastomotic aneurysms occurring at the femoral or popliteal level. In all cases recorded, the original replacement or bypass graft was patent at the time of surgery for the anastomotic aneurysm. It could not be documented in this series that the anastomotic pathology was playing any role in producing distal ischemia at the time of the reparative surgery.

Treatment

The surgical extirpation of these aneurysms is among the most tedious and difficult procedures for the peripheral vascular surgeon.

All but one of the lesions in the series were treated by surgical removal. The sole exception was a 73-year-old

TABLE 3. *Suture Material Used in Original Operation*

Suture Material	No. Aneurysms 1959–64	1964–69	1969–74
Braided Silk	6	1	0
Monofilament Synthetic	11	4	0
Braided Synthetic	1	7	6
Total 36 aneurysms	18	12	6

TABLE 4. *Time Interval From Original Operation to Appearance of Anastomotic Aneurysm**

No.	Site of Anastomosis	Time Interval	Aver. Time
8	Aortic Suture Line	1.5 Yrs–6 Yrs	3 Yrs
22	Femoral Suture Line	8 Mos–10 Yrs	2 Yrs
2	Iliac Suture Line	2 Yrs–4 Yrs	2.5 Yrs
3	Popliteal Suture Line	1 Yr–10 Yrs	4.5 Yrs
1	Dacron-Dacron Suture Line	2 Yrs	2 Yrs

* Average time—29 months.

man with a large dissecting aneurysm of the proximal aortic suture line. A Dacron woven bifurcation graft had been inserted 7 years previously following aortic aneurysmectomy done at another hospital. At the time of laparotomy the presenting pathology, with renal artery and iliac artery involvement, precluded, in the surgeon's judgement, any attempt at excision. The patient died of renal failure 6 days post-laparotomy. The remaining 35 lesions in this series were treated surgically.

Aortic Suture Line

As was described above, 6 of these aneurysms presented with aorto-enteric fistula and several of these cases were included in a previous report.[10] All 6 of these patients died in the hospital following excision of the aneurysm and replacement of the bifurcation graft. Although the operative procedure was successfully completed in all patients, the deaths were directly related to shock and/or sepsis in each case. Of the two remaining cases with anastomotic aneurysm of the proximal aortic suture line one was explored and not resected as described above. The remaining patient developed an anastomotic aneurysm 6 years following an end-to-side anastomosis for aorto-iliac occlusive disease. Successful replacement of his bifurcation graft was performed and he has remained well for 7 years.

Iliac Suture Line

The two patients in this category both had low back pain. In one the pulsatile mass was palpable in the left hypogastrium and in the remaining patient lumbar aortography revealed a moderate-sized lesion at the right external iliac end-side anastomotic site. In the latter case angiography, although not employed in most of our patients, proved to be of significant diagnostic benefit. The aneurysms in both patients were excised and arterial continuity restored. Both patients are asymptomatic 5 and 6 years postoperative.

TABLE 5. *Results: Surgical Removal Anastomotic Aneurysms*

Location	No.	Result			Amputation
		Death	Recovered		
Aortic Suture Line	7	6	1		0
Iliac Suture Line	2	0	2		0
Femoral Suture Line	22	0	22		4
Popliteal Suture Line	3	1	2		1
Dacron-Dacron Suture Line	1	0	1		0

Femoral Suture Line

Exposure and isolation of the graft, common femoral, superficial and profunda femoral arteries is tedious and technically, in some cases, very difficult. In each case the prosthesis was dissected free from the extensive cicatrix and the run-off vasculature carefully identified and the vessels individually taped. It must be emphasized that in most cases the deep femoral artery was the only patent vessel supplying the limb. Since the proximal femoral artery was occluded in 19 of the 23 patients it was divided in these instances and an end-end anastomosis performed between the interposed Dacron graft and the funnel-like remnant of the distal 1 cm of host common femoral artery.

It is to be emphasized that in all cases, except the one anastomotic disruption at the Dacron-Dacron anastomosis, an additional length of prosthetic graft was required to re-establish arterial continuity without suture line tension.

As noted in Table 5, in 4 of the 22 patients removal of the aneurysm and regrafting failed to maintain adequate distal arterial circulation and all 4 patients had amputations performed during their hospital stay. Eighteen patients were successfully treated and have remained well postoperatively for one to 8 years.

Popliteal Suture Line

In 2 of the 3 patients in this category, one required an above-knee amputation following unsuccessful excision and regrafting and the second patient died following an aortofemoral bifurcation bypass performed 16 days after the popliteal suture line aneurysm had been successfully excised with distal pulses re-established.

Comment

This report emphasizes that anastomotic aneurysms remain a continuing problem for the vascular surgeon. The appearance of such a lesion at the proximal aortic end-end suture line often is first heralded by erosion into the duodenum. This prompts one to consider all patients with retroperitoneal arterial prostheses who have any degree of gastrointestinal bleeding as candidates for emergency laparotomy in all but a very few instances. Delay in diagnosis and appreciation of the urgency of the complication has contributed to the very high operative mortality.

It is to be further emphasized that, despite the use of braided synthetic suture material, care in intimectomizing the recipient vessel, prevention of graft tension across joints and avoidance of anti-coagulation therapy in the immediate postoperative period, anastomotic disruption can occur in the absence of local sepsis. Gaspar[5] and Moore[6] respectively have scored the use of end-side anastomoses to the common femoral artery and prefer to place the distal anastomoses of the aortic bifurcation grafts to the external iliac vessel. Barker[2] has stressed mobilization of the proximal portion of the sartorius muscle to cover the proximal portion of the graft. It has been our experience that, with 6 anastomotic aneurysms occurring in patients operated upon in the last 5 years (a 1.9% incidence in 320 peripheral vascular reconstructions), anastomotic aneurysms still must be considered as a significant complication in peripheral vascular surgery. Despite the higher incidence of these lesions at the common femoral anastomosis we feel it pertinent to place the distal anastomosis of the aorto-femoral grafts in proximity to the profunda orifice. In our experience progression of atheromatous stenosis of the external iliac and femoral arteries has been a source of graft failure which has not been noted when the distal anastomosis has been placed in the common femoral vessel.

It is to be emphasized again that false aneurysms appearing in the femoral or popliteal suture lines lend themselves to early diagnosis and a very high percentage of good results from extirpative surgery.

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Incidental Splenectomy:

A Review of the Literature and the New York Hospital Experience

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981 consecutive splenectomies at The New York Hospital were reviewed. 18.9% were removed incidental to some other procedure, either to facilitate exposure or because of uncontrolled bleeding from capsular tears. The primary operation with which this was most frequently associated was gastric resection for peptic ulcer disease, accounting for 20.5% of the spleens so removed. Conversely, the incidental splenectomy was noted in only 0.91% of all gastrectomies and 1.4% of all left colectomies designated as nonradical procedures. It is therefore seldom a necessary procedure. Incidental splenectomy is more frequent when midline abdominal incisions are employed, less frequent with paramedian or left rectus splitting incisions. 85% of the spleens removed incidentally were grossly and microscopically unremarkable; lacerations most probably result from excessive manipulation rather than pathological changes predisposing to rupture. The postoperative morbidity and mortality is discussed and is felt to be increased significantly by the incidental splenectomy.

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THE PROXIMITY of the spleen to organs and tissues in the left upper quadrant may necessitate its removal during procedures in this region, either to facilitate exposure, to extend an operation, or secondary to injury with subsequent inability to control bleeding. In spite of the well known occurrence of incidental removal of the spleen, there remain relatively few studies documenting its frequency or contributing factors. Such information may prove helpful in understanding the morbidity and mortality associated with this procedure, and for this purpose the records of The New York Hospital have been reviewed.

All splenectomies performed at The New York Hospital between 1932 and 1971 were recorded. Included in this study as incidentally removed spleens are all spleens removed during an operation where splenectomy was not a part of the standard surgical description, or where extension of disease was not such as to make removal necessary. Each incidental splenectomy was evaluated as to the type and frequency of the primary procedure, gross and microscopic condition of the spleen, type of incision used, and postoperative complications, including any problems subsequent to the primary procedure and not simply those felt to be precipitated by the splenectomy itself.

Results and Discussion

The New York Hospital Experience

A total of 981 splenectomies were performed at The New York Hospital between 1932 and 1971 (Table 1). Of these, 433 (44.1%) were removed for the diagnosis and/or treatment of hematological disorders, 170 (17.3%) as part of a radical cancer procedure, 50 (5.1%) for trauma, and 143 (14.6%) for assorted hepatic and splenic abnormalities. Most importantly, 185 (18.9%) were removed incidental to other abdominal surgery, a figure which is consistent with reported series: Quan and Castleman[9] reviewed 70 splenectomies, all incidental to gastrectomy, and noted 18.5% to be secondary to operative trauma. In 748 consecutive splenectomies at Ohio State University, Zollinger *et al.*[13] found 58 removed as an adjunct to procedures for benign lesions and 23 for capsular tears, for a total of 81, or 10.4%. Fabri *et al.*[5] subsequently reviewed 1,944 splenectomies in the same in-

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stitution, apparently extending the previous series, and found that 18.9% were removed incidental to surgery for benign disease. Finney and Sumner[7] reported 13 of 116 consecutive splenectomies, or 11%, at Johns Hopkins Hospital to be secondary to iatrogenic tear. Peck and Jackson[8] reviewed 95 consecutive splenectomies at the University of Pittsburgh and noted 22, or 23%, to be necessitated by surgical trauma. And Rich *et al.*,[10] evaluating 925 splenectomies from California hospitals, found 244 removed for operative trauma (26%) and 46 (5%) to facilitate a benign procedure, for a total of 31%.

Incidental splenectomy in our series was most frequently associated with gastrectomy for peptic ulcer disease, accounting for 20.5% of the spleens so removed (Table 2). An additional 4 splenectomies were performed in association with other benign gastric surgery, including excision of a diverticulum, two gastrojejunostomy revisions, and a gastrostomy. Zollinger *et al.*,[13] discussing 58 splenectomies performed incidental to procedures for benign disease, noted that the procedures were "usually gastric resection for peptic ulcer." Rich *et al.*[10] found 37% of their incidental splenectomies to be associated with gastric surgery, and Devlin *et al.*,[4] reviewing 70 incidental splenectomies, noted 58.5% to be in conjunction with gastrectomy, predominantly partial. The removal of the spleen incidental to surgery on the stomach is thus well documented, whether it be as a consequence of mobilization for hemigastrectomy and Billroth I procedures as described by Zollinger,[12] or as a result of traction on the lienogastric ligament with disruption of the short gastric vessels and the splenic capsule in the hilar area, as proposed by Peck and Jackson.[8]

TABLE 1. *All Splenectomies at The New York Hospital, 1932–1971*

Incidental Splenectomy	185	18.9%
Primary Splenectomy	796	81.0%
Hematological Disorders	433	44.1%
ITP	157	
Congenital Hemolytic Anemia	148	
Acquired Hemolytic Anemia	56	
Hodgkins Disease	37	
Miscellaneous	35	
Radical Cancer Surgery	170	17.3%
Stomach	137	
Esophagus	13	
Pancreas	10	
Colon	6	
Miscellaneous	4	
Abdominal Trauma Rupture)	50	5.1%
Traumatic	38	
Blunt	31	
Penetrating	7	
Spontaneous	12	
Splenomegaly	33	3.4%
Splenorenal Shunt	20	2.0%
Banti's Syndrome	17	1.7%
After Splenoportogram	14	1.4%
Splenic Cysts	9	0.9%
Accessory Spleens	8	0.8%
Gaucher's Disease	8	0.8%
Splenic Artery Aneurysm	6	—
Liver Disease	5	—
Splenorenal Arterial Anastomosis	5	—
Hemangiosarcoma	2	—
Perisplenitis	2	—
Splenic Abscess	2	—
Miscellaneous	12	1.2%
Total	981	100.0%

TABLE 2. *Procedures with which Incidental Splenectomy was Associated*

Gastrectomy for peptic ulcer disease	38	20.5%
Repair hiatus hernia	18	9.7%
Left colectomy	18	9.7%
Bilateral nephrectomy	13	7.0%
Pancreatic surgery	12	6.5%
Vagotomy and drainage	11	5.9%
Exploration left upper quadrant	11	5.9%
Splenic flexure resection	11	5.9%
Left nephrectomy	10	5.4%
Transverse colectomy	6	3.2%
Left adrenalectomy or exploration	6	3.2%
Sigmoid resection	5	2.7%
Esophagectomy or esophageal surgery	4	2.2%
Resection abdominal aortic aneurysm	4	2.2%
Other colon surgery	3	1.6%
Exploration or biopsy left kidney	2	—
Right hemicolectomy	2	—
Revision gastrojejunostomy	2	—
Other gastric surgery	2	—
Total colectomy	1	—
Repair diaphragmatic hernia	1	—
Repair omphalocele	1	—
Measure portal pressure	1	—
Aortofemoral bypass	1	—
Splenic artery ligation	1	—
Cholecystectomy	1	—
Total	185	100.0%

The above incidence of 20.5% is not to suggest that incidental splenectomy frequently accompanies gastric surgery. Between 1932 and 1971, 4,411 gastric resections were performed at The New York Hospital,* or which 175 had associated splenectomies—137 planned as part of a radical procedure (Table 1) and 38 removed incidentally (Table 2). Thus 4,274 gastrectomies were considered "nonradical" (4411–137), representing an incidence of incidental splenectomy with gastric resection of 38/4274 or 0.91%. This does not include all other gastric procedures (gastrostomy, etc.) with which there were only 4 incidental splenectomies. This suggests that there is probably no anatomical reason necessitating removal of the spleen during gastric surgery, and with careful handling this added procedure can usually be avoided.

Procedures on the left kidney accounted for 25 of the incidental splenectomies, or 13.5%, and included 13 bilateral and 10 left nephrectomies, one biopsy, and one left renal exploration (Table 2). Three of the left nephrectomies were performed for malignant neoplasms,

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* No figures available for war years, 1941–1946.

TABLE 3. *Type of Incision Used*

Midline, upper or long	95
Left rectus	30
Left paramedian	17
Upper transverse	9
Left subcostal	9
Right subcostal	8
Thoracoabdominal	6
Right rectus	4
Left flank	5
Left thoracotomy	1
Left transverse	1
Total	185

all others being done for benign disease including hydronephrosis, renal calculi, or end-stage renal disease. All bilateral nephrectomies were done through midline incisions, while of the three radical nephrectomies, two used a thoracoabdominal and one a paramedian approach. Rich *et al.*[10] reported that 5% of all iatrogenic injuries to the spleen were associated with left nephrectomies, and Bozzell and Powell,[1] reviewing 63 operations on the left kidney, noted three splenectomies all associated with nephrectomies. We have included spleens removed for exposure as well as lacerations and, as noted, 16 of our nephrectomies used midline or thoracoabdominal incisions, which may have decreased exposure as compared to flank incisions. The four radical nephrectomies were accompanied by node dissections. Although comparative information for other series is not available, these factors may explain our higher incidence.

Eighteen incidental splenectomies were associated with hiatus hernia repair, for an incidence of 9.7% (Table 2). This is to be compared with 7% reported by Rich *et al.*,[10] 11% in Devlin's series,[4] and 28% in the study by Brown *et al.*[2] Of note is the fact that 5.9% of our incidental splenectomies accompanied vagotomy. While surgical manipulation in and around the esophagus for vagotomy is necessarily less than that for repair of a hiatus hernia, many of the maneuvers are similar, and attention to Weinberg's observation[11] regarding transabdominal vagotomies, that splenectomies "can be avoided if gauze packing is not used within the abdomen during the operation, and if the liver retractor is held properly so that it does not move to the left toward the spleen and its pedicle during exposure of the esophageal hiatus," may do much to reduce inadvertent splenic lacerations during hiatus hernia repair.

Left or transverse colon resections accounted for an additional 40 splenectomies, or 21.6% of those removed incidentally (Table 2). It is of interest that between 1932 and 1971, 274 "large bowel resections" (site not specified), 2,260 left, and 279 transverse colon resections were performed.* If the 6 radical colon procedures involving elective splenectomies (Table 1) are excluded, the remaining 2,807 colectomies comprise the total experience from which the above 40 incidental splenectomies were recorded, giving an approximate incidence of 1.4%. Thus, as in the case of gastric resection, if proper respect is paid to the left upper quadrant during procedures involving the left colon, splenectomy is seldom necessary.

The majority of incidental splenectomies in our series is thus found in association with gastrectomy for peptic ulcer disease, left or transverse colon resections, nephrectomies, and hiatus hernia repair. The remainder are associated with 15 different operations, including exploratory laparotomy, adrenalectomy, pancreatic and esophageal surgery, abdominal aortic aneurysm resection, and one cholecystectomy. The latter emphasize the respect one must give the spleen even in procedures not involving the left upper quadrant.

The most frequently employed incision was the midline, either upper or long, used in 52.4% of the cases (Table 3); only half this number was noted for left rectus and left paramedian incisions. If this is not coincidental, then better access to the left upper quadrant is obtained through these latter incisions, reducing the need for splenectomy to facilitate exposure, and at the same time giving more control over the factors likely to cause lacerations of the capsule—traction on the lienophrenic ligament, traction on the lienogastric ligament, traction on the splenic flexure of the colon with avulsion of the lienocolic ligament, or splenic puncture—described by Peck and Jackson.[8] Our findings, therefore, are not surprising, but point out the need for greater care in the exploration of the left upper quadrant through midline incisions.

Approximately 85% of the spleens removed incidentally were grossly and microscopically unremarkable (Table 4). Of the remainder the most frequent abnormality was hemosiderosis, noted in 10 cases. Incidental splenectomies, if not done for exposure, there-

TABLE 4. *Pathological Diagnosis of Spleens Removed Incidentally*

Unremarkable	157
Hemosiderosis	10
Passive congestion	6
Extramedullary hemotopoiesis	2
Lipid granulomata	2
Perisplenitis	2
Splenomegaly	2
Fibrosis and congestion	2
Nephroblastoma involving pancreatico-splenic ligament	1
Splenic artery aneurysm	1
Total	185

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* No figures available for war years, 1941–1946.

fore probably result from excessive manipulation of normal spleens rather than from an abnormal condition which makes them more friable of prone to laceration. Peck and Jackson[8] similarly could find no morphological change of the spleen predisposing to rupture.

Postoperative deaths and complications are listed in Tables 5 and 6. There were 28 deaths among 185 incidental splenectomies, for a mortality of 15.1%. This is significantly higher than the operative mortality for these cases in the absence of splenectomy, for with few exceptions (total colectomy for toxic megacolon, repair of omphalocoel, reduction of diaphragmatic hernia), all should be less than 10%. These 28 splenectomies included 19 removed for lacerations, nine which were felt to require drainage, 5 which resulted in accompanying injury to the distal pancreas, 4 which necessitated either a separate incision or extension of the initial incision, and 2 required reoperation for unrecognized bleeding. All, of course, prolonged the operating time.

In each of the 28 cases the exact contribution of the splenectomy to the operative death is difficult to assess. Reoperation is clearly a significant factor and, while prolonged ileus from the initial bleeding, persistent pancreatic drainage or left subphrenic abscess by itself was not established as a cause of death, in a case perhaps already complicated by other factors, the addition of any one of these problems may easily tip the balance.

A comparison of the operative mortalities of different series of incidental splenectomies shows our figure of 15.1% to be similar to others (Rich *et al.*,[10] 10%; Zollinger *et al.*,[13] 12.9%; Fabri *et al.*,[5] 14.0%; Peck and Jackson,[8] 18%). What increase is noted cannot be ascribed to an inherently higher mortality of the primary procedure, for the spectrum of operations in each series is similar. Nor can it be explained on the basis of operating conditions, patient population, or availability of diagnostic procedures, for all series were from large American university hospitals where these factors are rather uniform. The technical aspects of our 28 cases have been reviewed (Table 6), and indeed may explain what differences are observed. While this information is not available for other series, an increased frequency of drainage, more persistent attempts to repair lacerations, higher incidence of reoperation, or injury to contiguous organs may account for the 5.1% higher mortality over that reported by Rich *et al.*[10]

In addition to the 28 operative deaths, 64 complications were noted among 44 patients, including 6 cases of left subphrenic or subhepatic abscess and 7 thoracic complications (left pleural effusion, pneumonia, atelectasis). The latter most directly implicate the splenectomy, but many of the remainder including ileus, myocardial dysfunction, pulmonary embolus, and wound infection, while at sites distant from the left upper quadrant, nevertheless might be influenced by intra-abdominal bleeding, thrombocytosis, and the like accompanying splenectomy.

TABLE 5. *Complications Among Cases Involving Incidental Splenectomy*

Postoperative deaths	28	15.1%
Wound infection	15	8.1%
Left subphrenic/subhepatic abscess	6	3.2%
Ileus	4	2.2%
Left pleural effusion	4	2.2%
Congestive heart failure	3	—
Pulmonary embolus	2	—
RLL pneumonia	2	—
LLL pneumonia	2	—
Abdominal abscess (multiple)	2	—
Urinary tract infection	2	—
Dumping syndrome	2	—
Urinary retention	2	—
UGI bleeding	2	—
RUL atelectasis	1	—
Diabetes mellitus (difficulty in control)	1	—
Arterial occlusion rt. lower extremity	1	—
Myocardial infarction	1	—
Pancreatitis	1	—
Psychosis (steroid)	1	—
Atrial arrythmias	1	—
Wound dehiscence	1	—
Aspiration pneumonia	1	—
LLL atelectasis	1	—
Esophagitis	1	—
Thrombophlebitis	1	—
Fecal fistula	1	—
RLL atelectasis	1	—
Pancreatic fistula	1	—
Hypercalcemia	1	—
Total		100.0%

Thus, an overview of the postoperative course reveals it to be remarkable in 72 of 185 patients (44 patients with complications and 28 deaths) suggesting a rather significant contribution of the incidental splenectomy to the morbidity and mortality of these operations. This position is supported by others: Devlin *et al.*[4] feels that removing the spleen because of accidental damage during surgical operations "adds considerably to the operative morbidity as estimated by postoperative sepsis, chest infection rates, and length of inpatient stay." Quan and Castleman,[9] reviewing operative mortality among transthoracic gastrectomies with incidental splenectomies, noted "most (of the 18 mortalities) showed local thrombosis of the splenic vein from the site of ligation," and 5 cases demonstrated "more extensive involvement of the portal system." In 4, thrombosis had extended to intrahepatic branches to produce infarcts of the liver; . . . "in only one was death attributable to initial splenic vein thrombosis; the other 4 had multiple incomplete infarcts of the liver which, had death not occurred, might have produced symptoms of liver

TABLE 6. *Postoperative Deaths for Procedures Involving Incidental Splenectomy*

Primary Procedure	Drain LUQ	Reason for Splenectomy	Reoperation Required	Extension of Incision Necessary	Attempt to Repair Laceration	Injury to Other Organs	Time and Cause of Death
Total colectomy, Toxic Megacolon	Yes	Lac	No	No	No	Distal Pancreas	6 dys postop, coagulopathy
Renal Transplant	No	Exp	No	Yes**	No	No	4 dys postop, disseminated aspergillosis
Hiatus Hernia Repair	No	Lac	No	No	No	No	28 dys postop, perforated diverticula, bronchopneumonia
Subtotal Gastrectomy, Ca Antrum	Yes	Lac	No	No	No	Distal Pancreas	22 dys postop, myocardial infarction
Subtotal Gastrectomy, Bleeding Gastritis	Yes	Lac	No	No	No	No	1 dy postop, persistent UGI bleeding
Explor. Laparotomy for hemorrhagic pancreatitis	Yes	Lac	No	No	No	No	14 dys postop, hemorrhagic pancreatitis
Sigmoid Resection, Cecopexy, Sigmoid & Cecal Volvulus	Yes	Lac	No	No	No	Distal Pancreas	8 dys postop, RLL pneumonia
Bilateral Nephrect., Renal Transplant	Yes	Lac	Yes	No	No	Distal Pancreas	7 wks postop, subhepatic, subdia. abscess
Repair Gluteal Artery Aneurysm	Yes	Lac	Yes	No	No	No	11 dys postop, cardiopulmonary arrest
Repair Diaphragmatic Hernia	No	Exp	No	No	No	No	1 dy postop, UGI bleeding
Left Colectomy, Ca desc. Colon	No	Lac	No	No	Yes	Distal Pancreas	1 dy postop, gas bacillus infection
Resection Abdom. Aortic Aneurysm	No	Lac	No	No	No	No	7 dys postop, acute renal failure, pulmonary edema
Exploratory Lap., Ca Colon	No	Lac	No	Yes	Yes	No	9 dys postop, renal failure, metastatic ca
Hiatus Hernia Repair	No	Lac	No	No	No	No	1 dy postop, congestive heart failure
Aortofemoral Bypass	No	Lac	No	No	No	No	1 dy postop, thrombosed graft, shock
Vagotomy, Pyloroplasty	No	Exp	No	No	No	No	40 dys postop, bronchopneumonia, left CVA
Bilateral Nephrectomy, Renal Transplant	No	Exp	No	No	No	No	16 dys postop, chronic renal failure
Subtotal Gastrectomy, Bleeding Gastritis	No	Lac	No	Yes	No	No	14 dys postop, persistent UGI bleeding, hepatic coma
Hiatus Hernia Repair	No	Lac	No	No	No	No	13 wks postop, congestive heart failure, inadequate small bowel function
Left Colectomy, Ca desc. Colon	Yes	Exp	No	No	No	No	1 dy postop, pulmonary embolus
Bilateral Nephrectomy, Renal Transplant	No	Exp	No	No	No	No	7 dys postop, chronic renal failure

* Lac: Laceration Exp: Exposure
** Second incision, left subcostal

TABLE 6. (*Continued*)

Primary Procedure	Drain LUQ	Reason for Splenectomy	Reoperation Required	Extension of Incision Necessary	Attempt to Repair Laceration	Injury to Other Organs	Time and Cause of Death
Vagotomy, gastroenterostomy, Bleeding Gastritis	No	Lac	No	No	No	No	6 dys postop, persistent UGI bleeding
Completion Total Gastrectomy, UGI Bleeding	Yes	Lac	No	No	No	No	3 dys postop, LLL pneumonia
Subtotal Gastrectomy	No	Lac	No	No	No	No	8 dys postop, septicemia
Repair Omphalocoel, Partial Hepatectomy	No	Exp	No	No	No	No	1 dy postop, cardiopulmonary arrest
Bilateral Nephrectomy, Renal Transplant	No	Exp	No	Yes**	No	No	42 dys postop, bacterial endocarditis, septic emboli
Completion Total Gastrectomy	No	Exp	No	No	No	No	1 dy postop, persistent UGI bleeding
Resection Abd. Aortic Aneurysm	No	Lac	No	No	No	No	9 dys postop, cardiopulmonary arrest

* Lac: Laceration Exp: Exposure
** Second incision, left subcostal

failure." Zollinger *et al.*[13] remarking on the initial series of incidental splenectomies at Ohio State University, concluded that despite a 12.9% mortality, "when similar major surgical procedures without splenectomy are compared with those in which splenectomy was done, there is no evidence that removal of the spleen increases the surgical mortality." Fabri *et al.*[5] with a subsequent review of 1,944 consecutive splenectomies from the same institution, extending Zollinger's series, noted a 14% mortality and 44% morbidity for incidental splenectomy. They concluded that the addition of splenectomy to major surgical procedures plays a role in the morbidity and mortality beyond the anticipated risk for benign or malignant disease. Peck and Jackson[8] similarly feel that "the addition of splenectomy increases the operative risk, protracts convalescence, and may contribute to postoperative mortality." Others, however, have not had this experience. Ferguson *et al.*[6] in their series of 100 cases of 50% gastrectomy with vagotomy, with three splenectomies, noted that "this additional procedure (splenectomy) did not seem to produce any untoward results . . ." and Calamel *et al.*[3] discussing 3 deaths following surgery for UGI hemorrhage which involved iatrogenic laceration of the spleen, noted that none of these deaths, although the result of persistent postoperative bleeding, "were directly related to the splenic tear except for the general influence of mild to moderate hemorrhage and extension and prolongation of surgical operations." Analysis of our series of patients supports the conclusion that the incidental splenectomy does contribute significantly to the morbidity and mortality of the primary operation, and that without good reason this added procedure should not be lightly undertaken.

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The Influence of Oxyhemoglobin Affinity on Tissue Oxygen Consumption

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In an intact animal or patient, any shift in oxyhemoglobin affinity is inevitably associated with concurrent fluctuation in numerous other determinants of oxygen delivery. For this reason, the influence of hemoglobin affinity for oxygen on tissue oxygen consumption has been incompletely evaluated. The purpose of this study was to investigate the influence of oxyhemoglobin affinity as the sole variable of oxygen delivery in an isolated perfused canine hindlimb. A membrane lung system which allowed precise control of blood flow, temperature, arterial oxygen content and arterial pH was established. Twelve isolated canine hindlimbs were alternatively perfused with autologous stored (left-shifted) and fresh (right-shifted) blood in parallel perfusion systems. The 2,3-DPG concentrations, P_{50} and oxygen consumptions were significantly different in the two parallel perfusion systems. A decreased hemoglobin affinity for oxygen appeared to permit increased oxygen off-loading at the tissue level.

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THE PRONGHORN ANTELOPE (*Antilocapra americana*) can rival the cheetah with speeds up to 100 km/hr.[7] However, the antelope, unlike the cheetah, can maintain a speed of 65 km/hr for as long as 10 minutes.[4] In order to maximize oxygen delivery during periods of such high oxygen demand, the antelope should have evolved with a hemoglobin of low oxygen affinity. Such a hemoglobin would permit increased oxygen off-loading or release at the tissue level during stress. In fact, the P_{50} (oxygen tension necessary to half saturate hemoglobin) of antelope hemoglobin was found by Dhindsa and associates[5] to be 28.3 mm Hg. This value is 2 mm Hg above the P_{50} of human hemoglobin and antelope hemoglobin does therefore have a lower affinity for oxygen. Circumstantial evidence suggests that a therapeutic, purposeful decrease in hemoglobin affinity for oxygen might permit increased tissue oxygen delivery in critically ill patients. In an intact animal or patient any shift in oxyhemoglobin affinity is inevitably associated with concurrent fluctuation of numerous other determinants of oxygen delivery. The difficulty in isolating oxyhemoglobin affinity as a variable has heretofore prevented elucidation of its influence on tissue oxygen delivery. The purpose of this study was to evaluate the influence of oxyhemoglobin affinity as the sole variable of oxygen delivery in an isolated perfused canine hindlimb.

Methods

Twelve 25–30 kg (German Shepherd) dogs were used in this study. Twenty-one and 28 days prior to study the dogs were bled 450 ml into plastic bags (Fenwal^R containing 63 ml citrate phosphate dextrose) and the blood stored at 4 C. On the day of the study dogs were anesthetized with pentobarbital (20 mg/kg) intravenously. An isolated perfused hindlimb was prepared in a fashion reported previously from this laboratory.[8,10] The left femoral artery and vein were isolated. Cloth tapes were passed via the inguinal incision through a puncture site on the opposite side of the thigh. Tapes were then passed around both sides of the thigh to include all tissue except the femoral vessels.

Parallel perfusion systems were established (Fig. 1). Blood was pumped (Harvard Apparatus Model 1423) through membrane oxygenators (General Electric DuaLung 50). Blood temperature was controlled by circulating water from an adjustable temperature bath into the heat exchanger of the membrane oxygenators. The flow rates of nitrogen, carbon dioxide and oxygen into the membrane lungs were regulated independently.

The right femoral artery was catheterized and 900 ml of fresh blood removed into plastic bags (Fenwal^R containing 63 ml citrate phosphate dextrose). The autologous stored blood was placed in a 37 C bath and buffered to pH 7.40 with tri-(hydroxymethyl)-aminomethane.

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The fresh and stored autologous blood was then filtered into separate venous reservoirs. The blood was warmed to 37 C and debubbled. The left femoral vessels were cannulated and perfusion initiated with either fresh or stored blood. Partial ischemic time for the limb (from femoral artery ligation to onset of perfusion) was always less than 3 minutes. The isolating tapes were cinched down and central blood pressure rendered effectively zero by external fibrillation of the heart. Prior work in this laboratory[15] has demonstrated femoral arterial flow in the anesthetized 25 kg dog to be approximately 102 ± 10 ml/min. In order to ensure adequate oxygen delivery, pump blood flow was fixed at 140 ml/min during the entire period of study.

A temperature probe was placed via the femoral incision into adjacent subcutaneous tissue. The temperature of the blood was also measured in the venous reservoirs. Blood temperature remained approximately 0.5 C above subcutaneous tissue temperature. Blood temperature was set at 37 C by adjusting the water bath temperature and flow into the heat exchanger. Glucose was infused at 500 mg/hr into the venous line just proximal to the venous reservoir.

Following an initial equilibration period, arterial and venous blood samples were taken simultaneously. Oxygen tension, carbon dioxide tension and pH were measured on a blood gas analyzer (Corning, Digital 160). Hemoglobin concentration and saturation were measured on a cooximeter (Instrumentation Laboratories), precalibrated with dog blood. Glucose concentrations were measured on an Auto Analyzer (Technicon^R).

Oxygen uptake ($\dot{V}_{O_2}$) was calculated from CaO_2, CvO_2, and blood flow by the Fick relationship in the usual fashion. Systemic oxygen delivery (SOD) was calculated as arterial oxygen content times blood flow ($CaO_2 \times \dot{Q}$).

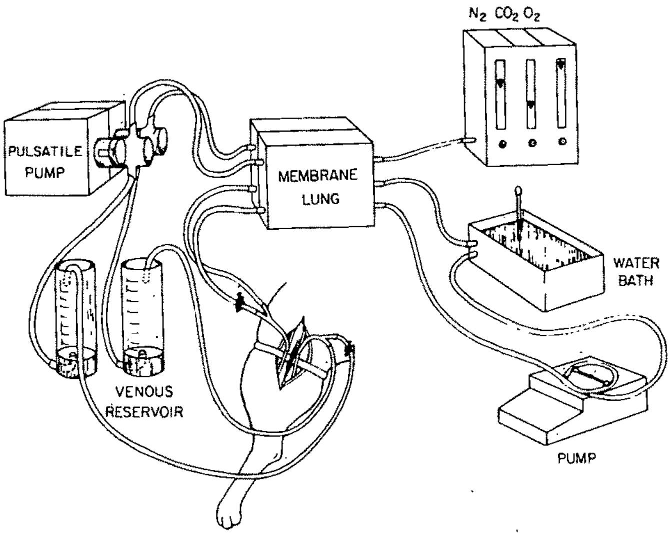

FIG. 1. Parallel perfusion system for canine hindlimb. Fresh and stored blood are placed in separate venous reservoirs. Blood is pumped through membrane lungs into femoral artery. Gas flow into lungs is independently regulated by N_2, CO_2 and O_2 gauges. Blood temperature is controlled by perfusing the lung heat exchanger with water from a variable temperature water bath.

Throughout the periods of observation, arterial pH was stabilized at 7.40 by appropriate bicarbonate infusion and alteration of carbon dioxide gas flow into the membrane lungs. At 10–15 min intervals, arterial and venous blood was sampled for calculation of $\dot{V}_{O_2}$ and SOD. Following four perfusion intervals (10–15 min each), the perfusate was switched from fresh to stored blood (or the reverse) and four more intervals were monitored in an identical fashion. This sequence was then repeated such that 16 observation intervals were accomplished as four groups (fresh-stored-fresh-stored) of four intervals.

The P_{50} of fresh and stored blood was determined in each instance by tonometry. Simultaneous oxygen tension and hemoglobin saturation determinations on several

TABLE 1. *Blood Perfusate Concentrations (Mean ± Standard Error of Mean)*

	Fresh Blood		Banked Blood	
	Initial	Final	Initial	Final
Calcium (mg %)	7.7 ± 0.4	7.6 ± 0.6	9.6 ± 0.5	10.1 ± 0.4
Phosphate (mg %)	5.7 ± 0.6	6.4 ± 0.4	8.8 ± 0.5	7.8 ± 0.7
Glucose (mg %)	187 ± 43	211 ± 14	190 ± 52	253 ± 40
Bun (mg %)	16 ± 1	14 ± 1	21 ± 4	21 ± 4
Uric acid (mg %)	1.8 ± 0.6	3.0 ± 1	2.0 ± 0.5	2.4 ± 0.4
Cholesterol (mg %)	77 ± 7	90 ± 7	110 ± 10	108 ± 12
Total protein (gms %)	3.3 ± 0.1	3.6 ± 0.1	4.2 ± .2	4.1 ± .3
Albumin (gms %)	1.8 ± 0.1	1.9 ± 0.1	2.0 ± .1	2.0 ± .1
Total bilirubin (mg %)	0.1 ± 0.02	0.1 ± 0.03	0.1 ± .05	0.15 ± .04
Alkaline phosphatase (mU/ml)	58 ± 7	48 ± 5	37 ± 9	35 ± 7
LDH (mU/ml)	74 ± 24	82 ± 43	350 ± 40	450 ± 45
SGOT (mU/ml)	20 ± 2	25 ± 5	63 ± 9	70 ± 10
Plasma Hbg (gms %)	0	0.1 ± 0.04	0.4 ± .2	0.7 ± .3
Sodium (mEq/L)	144 ± 5	140 ± 5	147 ± .3	145 ± 3
Potassium (mEq/L)	3.7 ± .2	4.0 ± .2	9.7 ± 1.5	9.6 ± 2.1

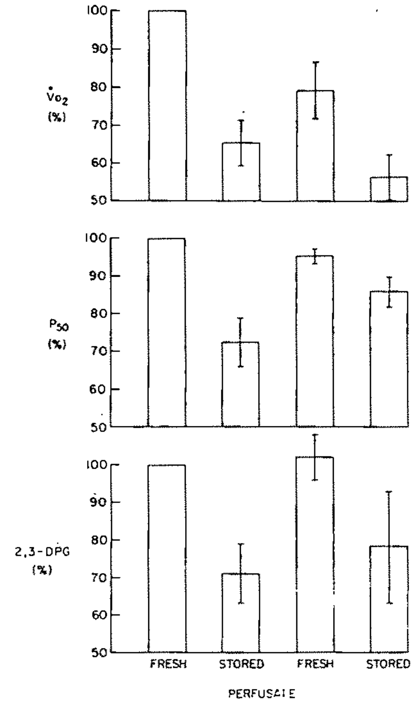

FIG. 2. Alternating perfusion periods with fresh and stored blood. Oxygen uptake ($\dot{V}_{O_2}$), oxygen tension necessary to half saturate hemoglobin (P_{50}) and 2,3-diphosphoglycerate concentration (2,3-DPG) are each presented as a per cent of the value for initial perfusion with fresh blood.

blood samples were corrected for pH and temperature and plotted. A straight line was used to connect the points on the steep portion of the dissociation curve. The oxygen tension corresponding to a hemoglobin saturation of 50% was noted as the P_{50}. The concentration of 2,3-diphosphoglycerate (2,3-DPG) was determined on alternate blood samples by the Sigma method (No. 665).

At the termination of each experiment, the hindlimb was amputated at the level of the isolating tapes. $\dot{V}_{O_2}$ was expressed as ml O_2 consumed per kg limb weight per minute.

As outlined above, 16 intervals of perfusion were divided into four periods. During each period of observation the limb was perfused with either fresh or stored autologous blood. Oxygen uptake, P_{50} and 2,3-DPG were evaluated as mean ± standard error of the mean for the values in each group. Differences between groups were assessed by Student's *t*-test for paired data.

Results

Table 1 presents initial and final concentrations of blood components for both fresh and stored perfusate. The phosphate, uric acid, cholesterol, alkaline phosphatase, LDH, SGOT, and plasma hemoglobin concentrations increased albeit insignificantly during perfusion with fresh blood. The calcium, phosphate, cholesterol, LDH, SGOT, plasma hemoglobin and potassium concentrations were significantly higher ($P < 0.05$) in stored than in fresh blood.

Oxygen uptake ($\dot{V}_{O_2}$), oxyhemoglobin affinity (P_{50}) and 2,3-DPG concentrations for each period of perfusion are presented in Fig. 2 and Tables 2 and 3. For purposes of comparison limb $\dot{V}_{O_2}$ during the initial perfusion with fresh blood is defined as 100% of oxygen uptake. Initial limb perfusion with fresh blood $\dot{V}_{O_2}$ was: 5.0 ± 0.76 ml O_2/kg/min (100%) mean ± SEM. Following conversion to stored blood $\dot{V}_{O_2}$ fell ($P < 0.01$) to 2.95 ± 0.33 ml O_2/kg/min (65.4 ± 6.8%). On reperfusion of the limb with fresh blood $\dot{V}_{O_2}$ recovered ($P < 0.01$) to 3.72 ± 0.41 ml O_2/kg/min (79.6 ± 7.8%). During the final period of perfusion with stored blood $\dot{V}_{O_2}$ again fell ($P < 0.01$) to 2.68 ± 0.34 ml O_2/kg/min (56.4 ± 6.9%).

The difference in oxyhemoglobin affinity (P_{50}) of fresh versus stored blood was statistically significant ($P < 0.001$). The 2,3-DPG concentrations of the fresh and stored blood were likewise significantly different ($P < 0.01$).

Blood temperature was greater than 36.5 and less than 37.5 C during all observation periods. During the four hour period of study, blood volume loss, as manifested by a decreasing level in the venous reservoir, was entirely accounted for by sampling.

Discussion

Tissue oxygen consumption is more than a function of intrinsic metabolic activity.[14] Oxygen delivery may also play an important role.[6] The amount of oxygen delivered to a tissue depends on three factors: 1) blood flow, 2) arterial oxygen content, and 3) oxygen availability ("releasability").

As the oxygen tension in water or plasma increases, the amount of oxygen in solution (oxygen content) rises in a linear fashion. The relationship between oxygen tension and oxygen content of a hemoglobin containing solution produces the familiar sigmoidal oxyhemoglobin dissociation curve (Fig. 3). The position of this curve however, is not fixed and many common environmental stimuli (temperature, organic phosphate concentration, pH) may shift the relationship to one of higher or lower hemoglobin affinity for oxygen.[13] Interestingly, when the O_2-Hbg dissociation curve of any blood sample is shifted, a constant relationship between the new position and the normal curve under standard conditions is preserved (at least between hemoglobin saturations of 20 to 80%).[12] Thus the ratio of oxygen tensions at any given hemoglobin saturation (between 20 and 80%) is constant throughout the whole curve. Therefore, by knowing a single point (simultaneous P_{O_2}, O_2 sat, pH and temp) for a test blood sample, the oxyhemoglobin dissociation curve for the test blood may be calculated from the normal human curve. Thus an entire curve can be generated from and defined by a single point. By convention, the oxygen tension necessary to saturate half the hemoglobin in solution (O_2 sat-50%) has been picked to define the position of the O_2-Hbg curve and is termed the P_{50}.

TABLE 2.

Dog	Blood	$\dot{V}O_2$		P_{50}		2,3–DPG	
		ml O_2/kg/min	%	mmHg	%	μM/gmHbg	%
A	Fresh	2.69	100	20.68	100	25.46	100
	Banked	2.04	75.8	18.28	88.4	15.73	61.8
	Fresh	2.32	86.2	21.78	105.3	20.54	80.7
	Banked	2.28	84.8	19.68	95.2	15.29	60 1
B	Banked	5.76	77.4	19.1	96.4		
	Fresh	7.44	100	19.82	100		
	Banked	5.08	68.3	20.62	108.0		
	Fresh	5.15	69.2	19.3	101.0		
C	Fresh	4.16	100	23.3	100		
	Banked	2.54	61.1	18.82	80.1		
	Fresh	3.70	88.9	23.32	100.1		
	Banked	2.47	59.4	19.68	84.5		
D	Fresh	3.30	100	22.15	100	26.65	100
	Banked	3.33	100.9	22.10	99.8	26.60	99.8
E	Fresh	2.15	100	23.67	100	20.65	100
	Banked	2.14	99.5	21.02	88.8	20.70	100.2
	Fresh	2.20	100.2	20.02	84.6	25.65	124.2
	Banked	1.59	73.9	21.28	89 9	24.10	116.7
F	Fresh	6.65	100	25.82	100	28.1	100
	Banked	2.30	34.6	20.68	80.1	28.7	102 1
	Fresh	5.77	86.8	23.42	90.7	28.8	102.5
	Banked	2.89	37.7	21.75	84.2	30.75	109 4
G	Fresh	3.01	100	28.6	100	19.5	100
	Banked	1.89	62.8	20.17	70.5	9.8	50.2
	Fresh	3.42	113.6	26.25	91.8	18.4	94.4
	Banked	2.28	75.7	21.87	76.5	6.75	34.6
H	Banked	2.55	81 5	22.18	93.4	21.5	85.3
	Fresh	3.13	100	23.76	100	25.2	100
I	Fresh	3.33	100	21.75	100	17.0	100
	Banked	2.50	75.1	18.50	85.1	8.2	48.2
	Fresh	2.82	84.6				
	Banked	2.41	72 4				
J	Fresh	10.11	100	25.62	100	22.12	100
	Banked	3.90	38.6	21.82	85.3	11.80	53.3
	Fresh	4.61	45.6	23.70	92.5		
	Banked	3.26	32.2	19.98	78.0		
K	Fresh	8.85	100	25.52	100	20.25	100
	Banked	2.24	25.3	17.10	67	5.9	29.1
	Fresh	3.45	39.0	22.92	89 8	20.35	100.5
	Banked	1.88	21.2	16.92	66.3	8.6	42.5
L	Fresh	5.24	100	23.75	100		
	Banked	4.17	79.6	23.16	97.5		

The P_{50} of normal human blood is 26.5 mm Hg. Fig. 3 represents a normal curve on the left (P_{50} = 26.5 mm Hg). It is apparent that 100 ml of blood with a hemoglobin concentration of 12 gms% will leave 3.7 ml of oxygen behind as it is pumped through the tissues. Again, assuming a fixed arteriovenous oxygen tension difference, when 100 ml of the right shifted (P_{50} = 31.5) blood is pumped through tissue it will leave 5.1 ml of oxygen behind (Fig. 3). This means that 37% more oxygen is released by the right shifted blood. Alternatively, a critically ill patient's heart could pump 37% less blood and deliver the same amount of oxygen by pumping right shifted blood. Though the therapeutic implications of these calculations have been recognized for almost 10 years, these concepts have been challenged as clinically irrelevant. The argument has been advanced that a small increase in hematocrit is comparable to the increase in oxygen delivery derived from any reasonable shift in the O_2-Hbg dissociation curve. The rightward shift of the dissociation curve from P_{50} = 26.5 to P_{50} = 31.5 (Fig. 3) would follow from a drop in pH from 7.4 to 7.25. Oxygen delivery is linearly related both to cardiac output and to hemoglobin

TABLE 3. *Mean ± SEM of All Dogs*

	$\dot{V}_{O_2}$		P_{50}		2,3–DPG	
Blood	ml O_2/kg/min	(%)	mm Hg	(%)	µM/gm Hbg	(%)
Fresh	5.0 ± 0.76	(100)*	23.7 ± 0.7	(100)†	22.8 ± 1.2	(100)*
Banked	2.95 ± 0.33	(65.4 ± 6.8)*	20.2 ± 0.5	(72.6 ± 6.1)	16.5 ± 2.7	(71.0 ± 8.2)
Fresh	3.72 ± 0.41	(79.6 ± 7.8)*	22.6 ± 0.8	(95.4 ± 2.3)	22.7 ± 1.9	(101.8 ± 5.9)
Banked	2,68 ± 0.34	(56.4 ± 6.9)	21.2 ± 0.6	(86.1 ± 3.8)	17.1 ± 4.6	(77.7 ± 14.8)

* $P < 0.01$
† $P < 0.001$

concentration. With a normal curve ($P_{50} = 26.5$) an increase in hemoglobin concentration from 12 gms% to 16.5 gms% would also result in release of 5.1 ml of oxygen to the tissues by 100 ml of blood. Therefore, an increase in hematocrit from 36% to almost 50% would be necessary to provide the same increase in tissue oxygen as the small O_2-Hbg dissociation curve shift depicted in Fig. 3. This mode of altering tissue oxygen delivery probably is relevant and operative in many clinical situations.

The most abundant organic phosphate in human erythrocytes is 2,3-diphosphoglycerate (2,3-DPG).[2] The concentration of 2,3-DPG in the red cell is similar to hemoglobin. In 1967 Chanutin and Curnish[3] documented a linear and inverse relationship between erythrocyte organic phosphate and oxyhemoglobin affinity. The concentration of 2,3-DPG progressively decreases in stored blood and after two weeks there is a virtual absence of this compound.[1] The hemoglobin affinity for oxygen in stored blood therefore increases with time of preservation. A change in any of the other determinants of hemoglobin oxygen affinity (pH, P_{CO_2}, temperature) may also influence the metabolic rate of tissues.[9,11] This concurrent alteration in tissue metabolism and oxyhemoglobin affinity renders the isolated evaluation of either difficult. For this reason we chose to shift the position of the oxyhemoglobin dissociation curve, in a clinically relevant manner, by storing autologous blood to induce 2,3-DPG depletion.

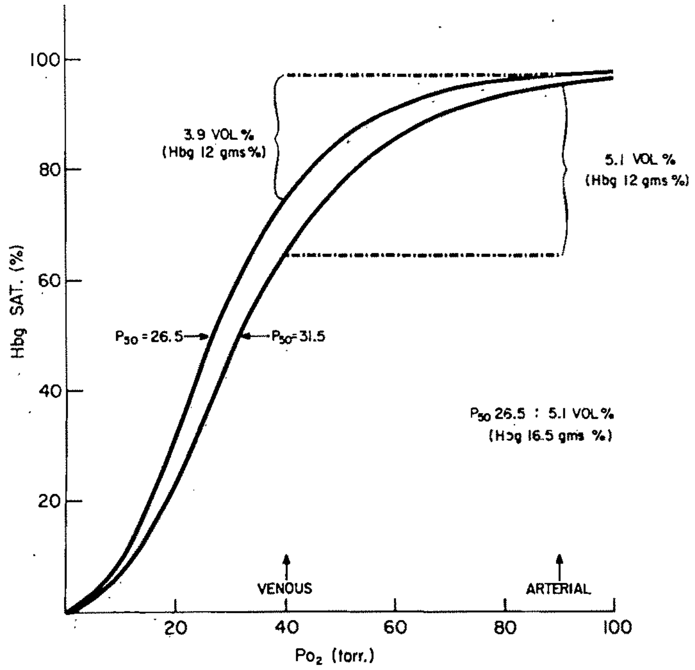

FIG. 3. Normal oxyhemoglobin dissociation curve ($P_{50} = 26.5$) on the left, with Hbg of 2 gms%, 3.9 ml O_2 is delivered per 100 ml of blood. With a shift of the O_2-Hbg curve to $P_{50} = 31.5$ or an increase in Hbg concentration to 16.5 gms%, 100 ml of blood will deliver 5.1 ml O_2.

Prior work in this laboratory[8] has demonstrated that the pH of the perfusing blood will influence limb oxygen uptake. Thus blood pH was fixed at 7.40 by continuously adjusting the carbon dioxide gas flow into the membrane lung. Blood samples in which the pH was less than 7.38 or greater than 7.42 were not included in the calculations. Likewise, by adjusting oxygen gas flow into the membrane lung and limb blood flow it was possible to maintain oxygen delivery to each limb (arterial oxygen content × blood flow) with less than ±5% fluctuation during the 16 intervals of observation. It was additionally determined that blood loss from the perfusion system, over and above that accounted for by sampling, of 40 ml over 4 hours (0.17 ml/min) could have been recognized. This would have a negligible influence on calculations of $\dot{V}_{O_2}$ and SOD involving flows of 140–160 ml/min.

As noted, the electrolyte and blood chemistry concentrations are not stable in stored blood (Table 1). No evidence is available however, to indicate that these chemical differences between fresh and stored blood will produce an acute and reversible change in tissue oxygen consumption.

With these qualifications, the oxygen uptake of an isolated canine hindlimb was examined under conditions of constant temperature, blood flow, pH, P_{O_2} and oxygen delivery but variable oxyhemoglobin affinity. In previous studies, in which the influence of pH[8,11] and pulsatile flow[10] on limb oxygen uptake were examined, the stability and viability of the preparation were established. There was a precipitous drop in limb $\dot{V}_{O_2}$ in response to perfusion with stored blood (high oxyhemoglobin affinity). Convincingly, there was also a statistically significant ($P < 0.05$) recovery of the limb oxygen uptake on reperfusion of the limb with fresh blood (Fig. 2, perfusion period 3). Additionally, when the limb was again perfused with stored blood, limb $\dot{V}_{O_2}$ decreased.

As has been noted previously[8,9,11] baseline oxygen uptake in ml O_2/kg limb/min may vary between animals. This variation is not related to sex and as in prior studies[8,10] is attributed to undefined differences between dogs. Thus for purposes of comparison, it is helpful to express the $\dot{V}_{O_2}$ for the various perfusion intervals as a percentage of the limb $\dot{V}_{O_2}$ observed during initial perfusion of each limb with fresh blood.

On reperfusion with fresh and stored blood during the third and fourth perfusion periods, some mixing of fresh and stored blood was inevitable. This mixing is manifested by an increase in both the P_{50} and the 2,3-DPG concentration of the stored blood (see Table 3 and Fig. 2).

After appropriate correction for blood pH and temperature,[12] the position of the oxyhemoglobin dissociation curve (as reflected by the P_{50}) has repeatedly been correlated with the 2,3-DPG concentration of the red blood cell.[1,3] In the study we again noted this relationship (Fig. 2, Tables 2 and 3). Recently, Yhap and colleagues,[16] using a system similar to ours, evaluated hemoglobin affinity for oxygen and indicated its influence on tissue oxygen uptake. Attempts to isolate this variable of oxygen delivery in previous clinical studies have been only partially successful. We conclude, however, that oxyhemoglobin affinity was the sole variable of oxygen delivery in this study, and hemoglobin affinity for oxygen was inversely related to limb oxygen uptake. A decreased hemoglobin affinity for oxygen appeared to permit increased oxygen off-loading at the tissue level.

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Pedal Vasomotor Tone Following Aortofemoral Reconstructions:

A Randomized Study of Concomitant Lumbar Sympathectomy

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A prospective randomized trial was undertaken to evaluate effects of lumbar sympathectomy as an adjunct to reconstructive surgery of the lower limb. The objective of this study was to assess the early postoperative effect of these procedures on pedal vasomotor tone. A pedal arterial resistance index (PARI) at rest was derived from the ratio of the ankle-digit systolic pressure gradient and pedal blood flow measured plethysmographically. Studies were performed on 32 normal individuals and pre- and postoperatively in 29 patients undergoing aortic reconstruction, 12 of whom were randomly chosen to have lumbar sympathectomy. The mean postoperative PARI in 17 patients who had reconstructions alone was 42 ± 7 (S.E.M.) units which approximated the preoperative PARI (43 ± 9 units) and normal control values (45 ± 6 units). In contrast, 12 patients who had a concomitant lumbar sympathectomy had a significant reduction in the postoperative PARI (8 ± 1 units, $P < 0.005$). These initial results indicate that the addition of lumbar sympathectomy to an aortic reconstruction may enhance blood flow to the foot by significantly reducing outflow resistance.

CONTROVERSY EXISTS concerning the benefit of lumbar sympathectomy as an adjunct to vascular reconstructive operations in the lower limb. In a recent survey of the current status of lumbar sympathectomy, Gillespie[5] stated that this procedure may be useful in conjunction with proximal arterial reconstructions when early pedal ischemia is associated with distal outflow resistance. However hemodynamic evidence that sympathectomy potentiates the effect of aortofemoral reconstruction in this situation is lacking.[11,13]

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A prospective randomized trial was undertaken in patients undergoing aortic reconstruction with and without concomitant sympathectomy. One of the objectives of this study was to evaluate the effect of these operations on pedal vasomotor tone. A pedal arterial resistance index (PARI) was used to determine the early postoperative effect of lumbar sympathectomy in patients undergoing proximal arterial reconstructions. Initial results of this investigation are presented and discussed.

Patients Studied

Thirty patients underwent aortofemoral bypass, aortoiliac endarterectomy or aortic aneurysmectomy; 13 of these patients were randomly assigned by computer to undergo a concomitant bilateral lumbar sympathectomy. The nature, objectives and risks of the study were carefully explained to the patients who freely consented to this investigation. There were 20 men and 10 women, who ranged in age from 37–78 years (mean 60 years). Eighteen complained of severe claudication, 6 had rest pain and/or gangrene, 10 had abdominal aortic aneurysms, 4 of which were asymptomatic. All suffered from atherosclerosis and two were diabetic. A detailed clinical examination was carried out in each patient and extensive vascular disease was confirmed by arteriography. Thirty-two patients (64 limbs) who had no clinical evidence of vascular disease documented by history, normal pulses and absence of bruits were studied as a control group. There were 28 men and 4 women with a mean age of 48 years (range 21 to 82 years).

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Method

The pedal arterial resistance index (PARI) was derived from the following formula:

$$\text{PARI} = \frac{\text{Pa} - \text{Pd}}{\text{F}} \text{ mm Hg/cc/min/100 cc tissue (hereafter, units)}$$

where

Pa = ankle systolic pressure; mm Hg
Pd = digit systolic pressure; mm Hg
F = flow through the foot; cc/min/100 cc tissue

These investigations were carried out in an air-conditioned room, the temperature of which ranged from 22–23 C. Patients rested for 30 min prior to evaluation and only the feet were exposed to the ambient air during the procedure.

The systolic pressure of the great toe was determined using an electrically-calibrated strain gauge plethysmograph. A mercury-in-silastic strain gauge was placed around the distal phalanx at the level of the base of the nail. A blood pressure cuff (inflatable bladder 7 × 2 cm) was applied to the proximal phalanx of the digit. The ankle systolic pressure was measured using a pneumatic cuff (bladder 40 × 9 cm) at the ankle and a strain gauge placed around the middle of the foot. The cuffs in turn were inflated above systolic pressure and deflated slowly. Systolic pressures were noted when the strain gauge registered on a pen recorder a change in volume. Pedal blood flow was determined by a venous occlusion technique. The venous occlusion pressure was determined by inflating the ankle cuff to different pressures (20–60 mm Hg range) and noting that pressure which resulted in the greatest initial rate of change in recorded pedal volume. The ankle cuff was inflated rapidly to the venous occlusion pressure and the change in volume was recorded. Pedal blood flows were determined at 6–10 sec intervals and were repeated 5 times. The flow (cc/min/100 cc of pedal tissue) was calculated from the mean of the initial upslope of the recorded change in volume.

The PARI was determined at rest in both feet preoperatively and 7–10 days postoperatively in the 29 patients included in the series. Normal values were obtained in 32 patients who had no evidence of vascular disease.

Results

The results of the PARI in control patients and in those patients who underwent aortic reconstructions with or without lumbar sympathectomy are illustrated in Fig. 1. The normal mean PARI was 45 ± 6 (mean ± S.E.M.) units. Preoperative values of the sympathectomized and non-sympathectomized groups were 43 ± 9 and 40 ± 4 units respectively and did not differ significantly from control values ($P > 0.1$). The postoperative PARI in 17 patients who had reconstructions alone was 42 ± 7 units which approximated the peroperative PARI. Twelve patients had a bilateral lumbar sympathectomy as an adjunct to their reconstruction and had a significant reduction in the PARI postoperatively, 8 ± 1 units, ($P < 0.005$) which was also decreased compared to that of the non-sympathectomized group of patients ($P < 0.001$).

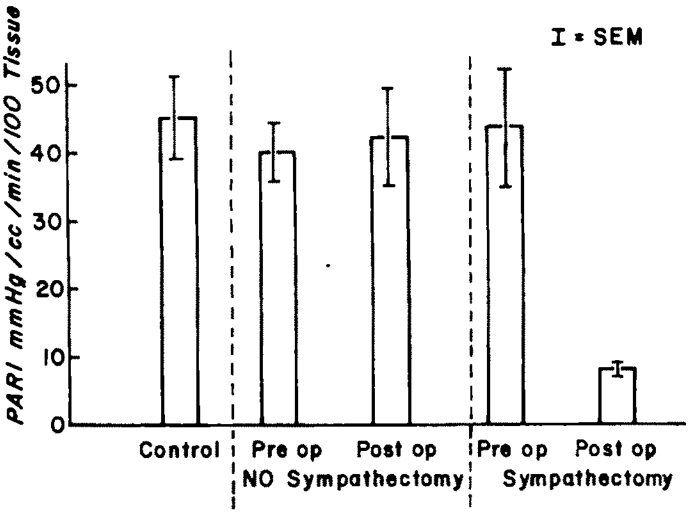

FIG. 1. Pedal vasomotor tone following aortofemoral reconstructions: a randomized study of concomitant lumbar sympathectomy.

One patient, who had a sympathectomy, failed to improve immediately following surgery due to thrombosis of the distal collateral circulation. He subsequently underwent bilateral above-knee amputations at which time his aortofemoral graft was still patent.

Discussion

Many authors have advocated the use of lumbar sympathectomy as an adjunct to reconstructive surgery of the lower limb.[6,7,15,16] However some reports question its value in this situation.[1,4,12,17]

Gillespie[5] suggested that sympathectomy may benefit patients undergoing aortic reconstructions who had combined aortofemoral and popliteal occlusions. Proximal reconstruction is the treatment of choice in this situation since results are much superior to femoropopliteal operations alone. However, if the foot is in an early state of ischemia, a concomitant sympathectomy may increase blood flow to the distal extremity by reducing outflow resistance. Blain and colleagues[2] proposed that lumbar sympathectomy when combined with a reconstructive procedure may forestall amputation if a graft or endarterectomy should fail. Casten, Sadler, and Foreman[3] reported that sympathectomy had a beneficial effect on the patency of arterial anastomoses in animal experiments. This observation has been supported by clinical studies.[2,15–17] May and associates[8] indicated that a concomitant sympathectomy may prevent thrombosis at the site of actual reconstruction by virtue of the increased flow it produces in normal or reconstructed arteries. Weale[16] observed that sympathectomy caused a marked reduction in the peripheral resistance of the major vessels of the outflow tract following reconstructive surgery. Kountz and Cohn[6] reported that the post-occlusion reduction in blood flow following aortic reconstruction was reversed by sympathectomy.

Others have observed no difference in the early patency of arterial grafts for limb salvage when sympathectomy was combined with a reconstructive procedure.[13,17] Szilagyi[13] stated that "the evidence must be brought in by those who make the claim for the effectiveness of the procedure rather than by those who will not accept the claim until proof is at hand." Simeone and Husni[10] published a detailed clinical study showing that a period of hyperemia occurred following reconstructive procedure. In these patients the skin was warm and dry, and the vasculature did not respond to environmental stimuli producing vasoconstriction. This sympathectomy-like effect, often lasting for a long period of time, was also noted by Strandness.[12]

Terry and associates[14] observed that the period of hyperemia was extremely short following femopopliteal bypasses and a stable flow level was rapidly achieved. They confirmed that patients undergoing femoropopliteal reconstructions had a higher failure rate due to low graft flow states than others did in whom an additional concomitant sympathectomy was performed.

There are two factors governing the outflow resistance in the lower limb; these are the fixed unyielding resistance due to the disease process and the variable arteriolar resistance controlled to a great extent by the sympathetic nervous system. Previous studies[9] in our vascular laboratory have shown the PARI to be a reliable monitor of pedal vasomotor tone. Resting preoperative values vary in both the normal and diseased limbs due to the individual limb response to physiological and environmental stimuli, providing that a fixed resistance is absent.

The results of this investigation indicate that patients who underwent proximal reconstructions alone had a postoperative PARI which approximated normal resting values. The prolonged peripheral vasodilation reported by others following reconstructive vascular operations of the lower limb has not been evident in our study. These patients had no obvious postoperative hyperemia of their limbs and had normal vasomotor tone in their feet. In contrast those patients who had a concomitant lumbar sympathectomy had dilated hyperemic feet.

To date there has been one early postoperative failure. This patient underwent an aortic reconstruction with a concomitant bilateral lumbar sympathectomy. He had severe multisegmental distal arterial disease by arteriography; postoperatively he suffered thrombosis of the distal collateral circulation despite adequate heparinization. However the aortofemoral graft was still patent at the time of amputation.

Lumbar sympathectomy significantly reduces the vasomotor tone of the foot in the early postoperative period in patients undergoing aortic reconstructive procedures. Such peripheral vasodilatation may enhance blood flow through the reconstructed segment. We would emphasize however that its effect on early and late graft patency in our series will not be known until more patients have been followed for a much longer period of time.

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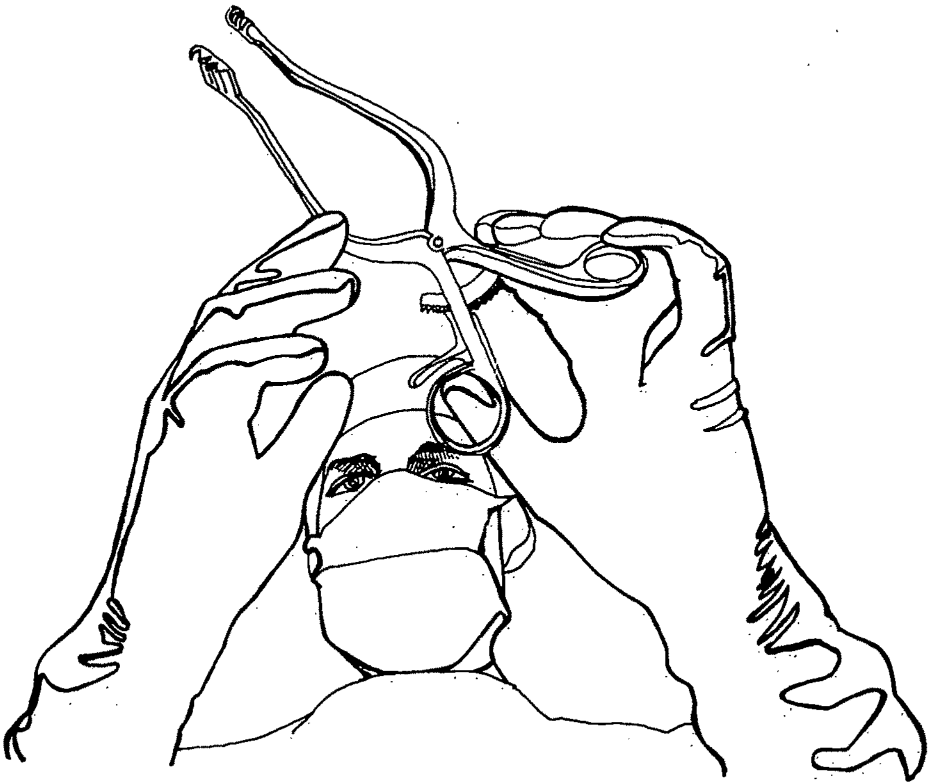

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Radiotherapy	Prior to initiating radiotherapy, once at midpoint and/or upon completion of radiation	To monitor the effects of radiation[1,2,5,6]
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	During Short-term Follow-up After Therapy	
All types	Every 1 to 2 months during the first 6 months following therapy	To provide a basis for the reevaluation of therapy and/or an early indication of recurrence or progression of disease[1,2,8]
	During Long-term Follow-up	
All types	Every 6 to 12 months	To provide an early indication of recurrence or progression of disease[1,4,9,10]
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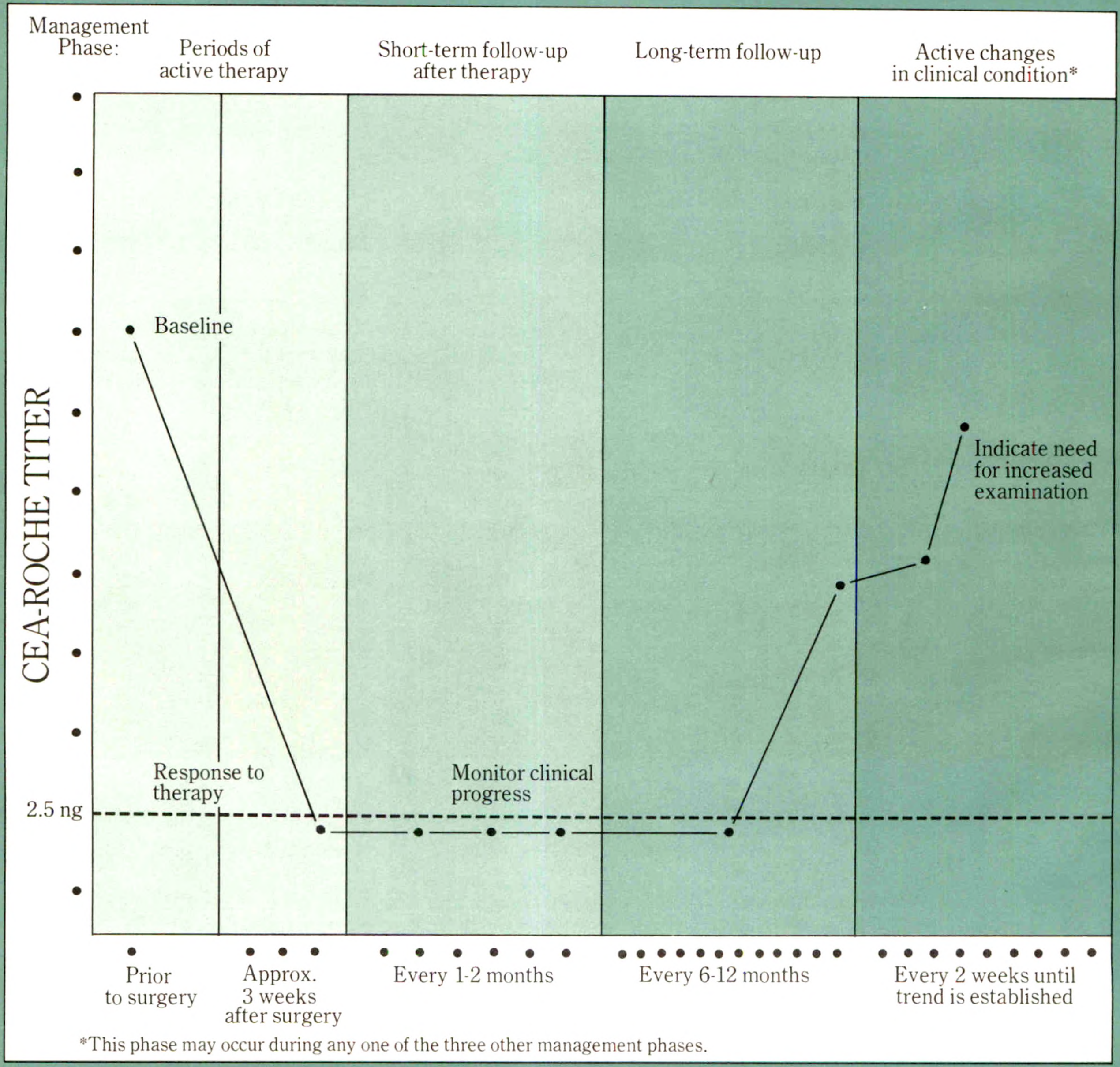

*This phase may occur during any one of the three other management phases.

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Diagnosis and Surgical Treatment of Mediastinal Parathyroid Tumors

M. ROTHMUND, L. DIETHELM, H. BRÜNNER, F. KÜMMERLE

Experience and problems in the localization, diagnosis and surgical treatment of mediastinal parathyroid tumors are reported. Arteriography, pneumomediastinum and, especially, selective blood withdrawal with assay of parathyroid hormone, have proven valuable to the authors. Scintigram, intravital staining methods and venography are less productive. Retrosternal parathyroid tumors that can be removed from a Kocher incision should not, for practical reasons, be classified with the mediastinal tumors. The authors recommend the one-phase operation. If, after an intensive search of the neck and behind the sternum, no tumor has been found, it is advisable to incise the sternum step by step and revise the anterior mediastinum in the same session.

From the Surgical University Clinic, and the Institute for Clinical Radiology, University of Mainz, Germany

THE SEARCH for parathyroid tumors in primary hyperparathyroidism still presents problems despite numerous advances in preoperative diagnostics[3,7,17,23,24,38] and considerable standardization of procedures for surgical exploration.[21,28,31,32] Difficulties arise especially if examination of the entire neck region is fruitless and dystopic localization of the parathyroid tumor in the mediastinum is to be expected.

The intramediastinal location of parathyroid glands is of ontogenetic origin. They develop during ontogeny from the outgrowths from the dorsal epithelium of the third and fourth branchial pouches. On their way to the lower neck region, the parathyroids developing from the third branchial pouch overtake those stemming from the fourth and may generally be found in the area of the lower pole of the thyroid. In about one-fifth of the cases they are entrained into the anterior mediastinum by the thymus, which springs from the ventral epithelium of the two branchial pouches. They may be found inside the thymus gland, adhering to its capsule or, without any relation to it, in the anterior or, rarely, posterior mediastinum. Kurtay and Crile[18] found that among 120 patients who were operated on because of primary hyperparathyroidism or thymectomized for purposes of immunosuppression, 23 (19%) had ectopic parathyroid glands in the anterior mediastinum. Eighteen parathyroids were found in the thymus gland or in immediate relation to it. Wang,[39] on the basis of autopic studies, also cited a 20% incidence of intramediastinal parathyroids. The fact that a sizable number of normal parathyroid glands are likewise located in the anterior mediastinum militates, in our estimation, against the view held by many authors[5,21,31] that because of their greater weight the parathyroid tumors are displaced from their normal position into the anterior mediastinum by force of gravity.

Generally, the incidence of intramediastinally localized parathyroid tumors is reported to be 5 or 20% (Table 1). The reason for these strikingly divergent figures may lie in varying definitions and interpretations by different authors of the localization.

If all tumors that are situated behind the superior sternal margin or lower are subsumed under the term "mediastinal," they will be found to account for one-fifth of the total number in nearly all groups. This statement is correct from a topographic-anatomical viewpoint but is not relevant to the surgical practice. We would suggest that the term intramediastinal be applied to only those tumors which require sternotomy or thoracotomy for extirpation. On the basis of this interpretation the percentage of intramediastinal parathyroid tumors initially cited by Nathaniels et al.,[21] for example, would be reduced to 5%, for extirpation of the tumor required sternotomy in only 19 of their 400 patients.

From 1965 to 1974 we treated 50 patients with primary hyperparathyroidism at the Surgical University Clinic in Mainz. Fifty-six parathyroid tumors were found.

Submitted for publication April 15, 1975

TABLE 1. *Incidence of Intramediastinal Parathyroid Tumors Reported in the Literature*

Author	No. of Cases	Intramediastinal	%
Cope, 1941	49	9	18.4
Norris, 1947	322	17	5.3
Hellström, Ivemark, 1962	138	8	5.8
Romanus et al., 1967	130	5	3.8
Nathaniels et al., 1970	400	84	21
Scholz et al., 1973	abt. 1000	14	1.4
Kümmerle et al., 1974	50	7	14

Thirty-three tumors were typically localized near the superior or inferior pole of the thyroid. Ten were found, after subtotal thyroidectomy, to lie within the thyroid gland. Six tumors could be displaced and removed from their retrosternal position by means of Kocher's operation (Table 2). In 7 patients exploration of the anterior or posterior mediastinum was necessary for removal of the parathyroid tumor (Table 3). Compared with the literature, this rate is very high. The reasons are that we refuse deep retrosternal manipulations without visual control, and, on the other hand, that many patients are referred to us after unsuccessful neck operation. Of the 7 patients mentioned here, 3 had been operated on in another hospital before.

Localization Techniques

Inasmuch as parathyroid tumors are seldom palpable, the techniques of localization are of great importance. Angiography, pneumomediastinum and, most recently, selective determination of parathyroid hormone after withdrawal of blood from the thyroid veins have proven to be useful methods. In our experience, selenomethionine scintiscanning and intravital staining with toluidine blue are less productive (Table 4).

Scintiscan Studies

Although good results in the visualization of parathyroid tumors with ^{75}Se-methionine have been reported,[2,13] statistically validated data are scanty.[1,26,31,40] Even after introduction of the photoscanner the percentage of positive results did not increase. We had selenomethionine scans made in 21 patients but were able to confirm the indicated localization operatively in only 4 cases. The examination failed in the case of small, difficulty localizable tumors displaying little hormonal activity. Nevertheless this method seems to us to be justified since, apart from the relatively high radiation load, direct complications are rare. Conceivably, better results can be obtained after stimulation of the parathyroid tumors with glucagon.[2]

Arteriography

Good results have occasionally been obtained with angiography of parathyroid tumors by injection of contrast media into the thyrocervical trunk or into the inferior thyroid artery. Borm and Werner[4] confirmed the localization of 13 adenomas in 17 patients operatively. They used the method that Seldinger[33] described in 1954, in which the contrast medium is injected via the ulnar artery into the subclavian artery. They always performed the puncture bilaterally in one session. Kuntz and Goldsmith,[17] used the approach from the two cubital arteries and through superimposed projections of angiograms and parathyroid scans succeeded in localizing 12 of 15 solitary adenomas in 15 patients, and 4 of 6 multiple tumors in 3 cases. Silinkova-Malkova,[36,37] who initially employed the same technique, obtained better results after using the femoral artery approach and injecting the radiopaque medium via an Oedmann catheter into the subclavian artery ahead of the thyrocervical trunk.

Selective visualizations of the thyrocervical trunk from the femoral artery according to the Hettler technique were performed in 16 of our patients. A parathyroid tumor was found, and its presence operatively confirmed, in 7 cases. This variant is considered technically difficult but promises better results than the Seldinger method. It is, however, associated with complications of the type that have been described with vertebralis angiography. Hellström and Ivemark[14] reported cerebral complications in 2 out of 9 angiographed patients. Ackermann and Winer[1] as well as Wang[40] also mentioned complications due to the method. Among our patients, three developed cerebral complications. Signs of an acute cerebral circulatory disturbance, subsequently reflected in focal EEG symptoms, occurred in a female patient during the examination. She died a few days after the examination without having been operated on. Another female patient developed a homonymous hemianopia, and another, a male patient, suffered for several weeks from CNS-related vomiting. For these reasons we tend to prefer the less hazardous examination via the ulnar artery.

Pneumomediastinum

Tomograms of the mediastinum following transtracheal puncture in insufflation of carbon dioxide gas were

TABLE 2. *Localization of 56 Parathyroid Tumors in 50 Patients*

Localization	Number
Eutopic	33
Ectopic	
intrathyroid	10
retrosternal	6
intramediastinal	7

TABLE 3. *Mediastinal Parathyroid Tumors: Findings in 7 Patients*

Case	Age, Sex	Type	Prior Surgery	Localization Technique	Approach	Localization	Histology
1	36, M	Parathyrotoxicosis	Neck exploration (neg.)	none	Median sternotomy	in thymus tissue, on radical extirpation of mediast. connective & adipose tissue	Adenoma
2	47, M	Osseous, renal, gastrointestinal	Neck exploration, removal of 1 parathyroid gland 2nd neck exploration & examin. of anterior mediastinum (neg.)	Angioscintiscan + angiography + pneumomediast. + toluidine blue staining ∅ (Figs. 1–3)	Thoracotomy 4th intercostal space rt.	Posterior sup. mediastinum	Struma aberrata vera with parathyroid gland (Hyperplasia)
3	52, F	Osseous, renal	None	Angiography ∅	Neck incision and median sternotomy	Behind V. subclavia sin., surmounting trachea	Adenoma
4	55, M	Osseous, gastrointestinal	Neck explorn., removal of 2 hyperplastic parathyroids explor. of retrosternal space	Scan ∅ Angiography (+) Pneumomediastinum +	Thoracotomy 4th intercostal space rt.	Posterior superior mediast.	Hyperplasia
5	65, F	Osseous, renal, gastrointestinal	Neck exploration	Angiography ∅	Neck incision and partial sternotomy	Before aortic arch	Adenoma
6	67, M	Osseous, renal, gastrointestinal	Neck exploration, removal of intrathyroid hyperplastic gland	Scan + Venography + Pneumomediastinum +	Partial sternotomy	Behind corpus sterni	Hyperplasia
7	50, F	Renal	None	Scan ∅ Venography ∅	Neck incision and partial sternotomy	in left venous angle	Adenoma

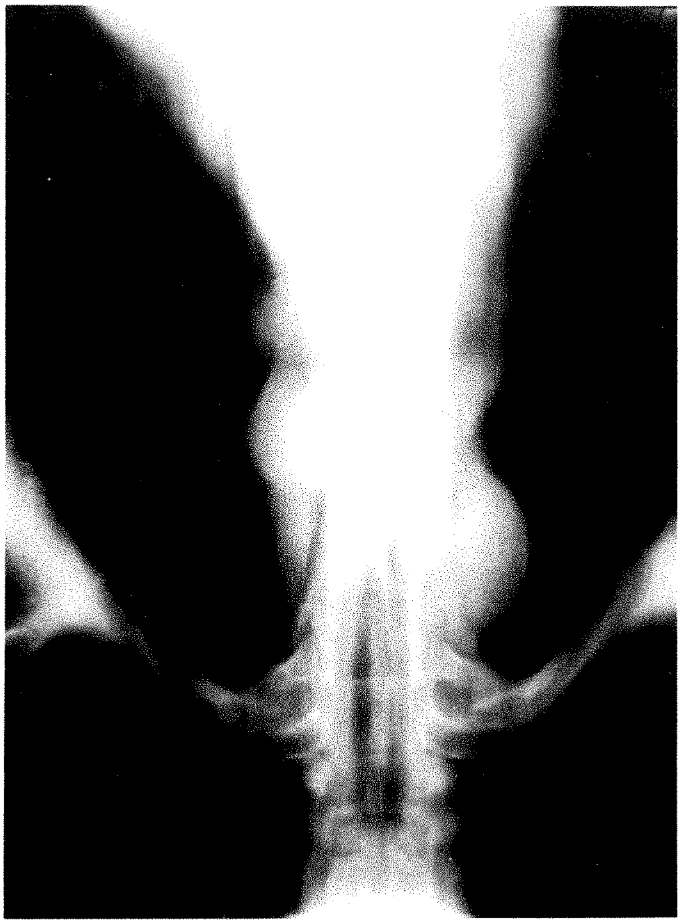


FIG. 1a. (Case 2 of Table 3) Demonstration of a right posterior mediastinal tumor by pneumomediastinum in a case of persistent primary hyperparathyroidism after exploration of the neck (twice) and the anterior mediastinum.

prepared in 8 of our patients. In 3, we were able to demonstrate tumors in the mediastinum by this method. In 2 cases these were tumors in the posterior superior mediastinum; the third was a parathyroid adenoma, weighing 12 g, that was located directly behind the corpus sterni. One tumor in the posterior mediastinum was detected angiographically before surgery. However, the films obtained in the anteroposterior direction of the beam had led to the assumption that the adenoma was located retrosternally. The pneumomediastinum was not prepared until after the unsuccessful exploration of the retrosternal space. This permitted accurate localization of the tumor and its removal by right-sided thoracotomy.[6]

Pneumomediastinum is a method that is not very stressful, unlikely to cause complications, and at the same time effective. Silinkova-Malkova[36,37] detected by this method 33 of 44 parathyroid tumors in 40 patients. All adenomas localized in the mediastinum were reliably demonstrated. Difficulties are to be anticipated only in the case of parathyroid tumors situated in the cervical region behind the superior thyroid poles. Pneumomediastinum is advisable also after exploration of the neck and the anterior mediastinum. Yet the tumor must be at least about 10 mm in diameter.

Vital Staining With Toluidine Blue

Since the selective staining of parathyroid glands, pancreas and corpus ventriculi mucosa after intravenous administration of toluidine blue in the dog had been described, it was logical that an attempt should be made to achieve vital staining of the parathyroids in man, either by direct preoperative intravenous infusion or by intraoperative injection into the inferior thyroid artery.[15] More recent studies in dogs confirmed that the dye is selectively concentrated in the parathyroids. By comparison with the neck musculature, the concentrations reached 30:1 and 42:1, respectively.[20] The observations in humans are contradictory.[15] We administered

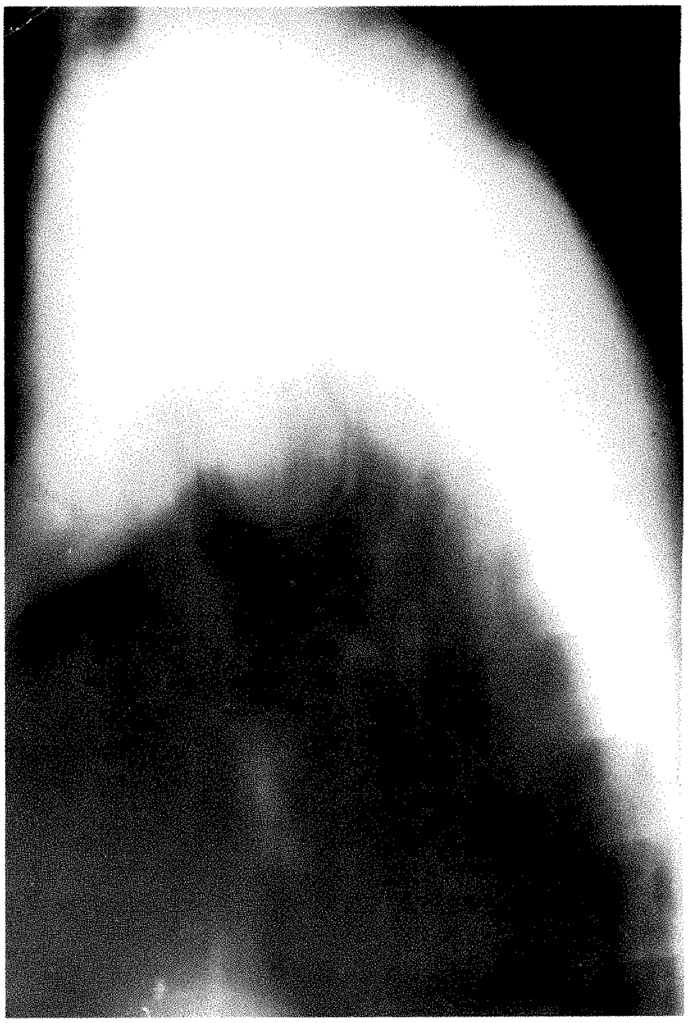
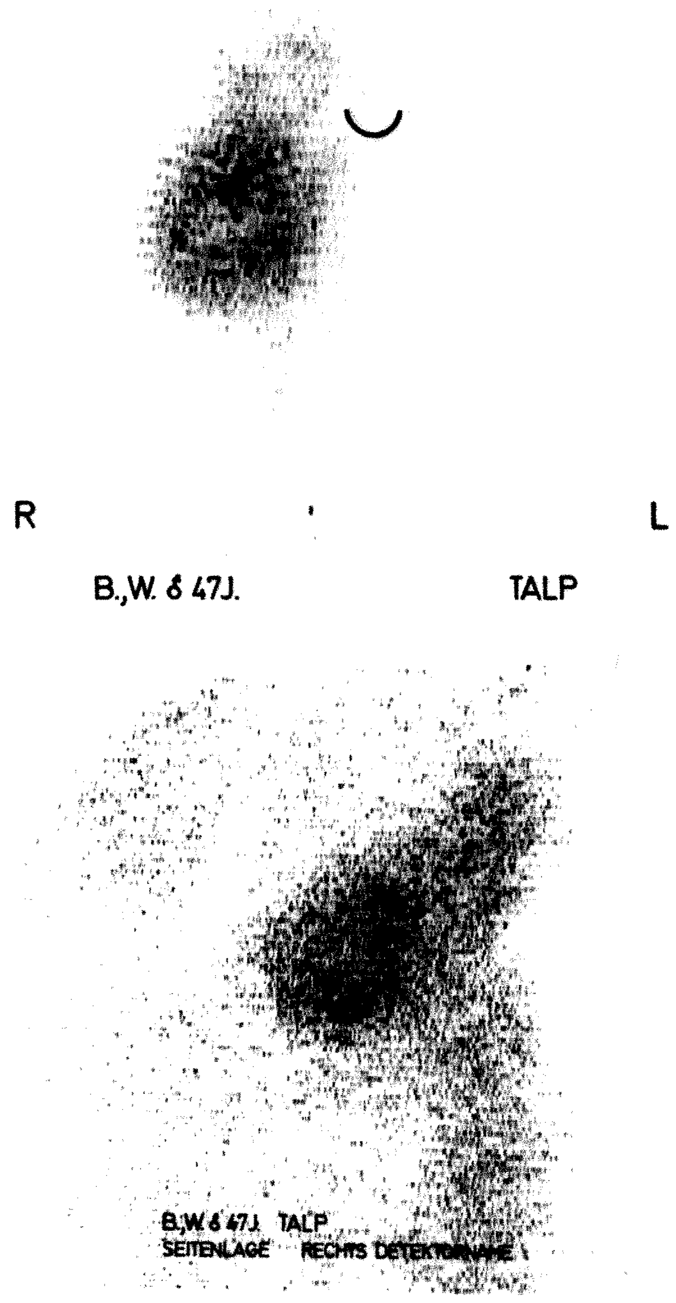


FIG. 1b. See legend for Fig. 1a.



FIGS. 2 a and b. (same case as Fig. 1): The same tumor is shown by angioscanning. A macromolecular radioisotope (TALP) is injected in the thyreocervical trunc after transfemoral catheterisation.

toluidine blue preoperatively by infusion to 6 patients at a concentration of 6 mg/kg body weight during one hour and failed to achieve a sure selective staining of the subsequently localized adenoma in all of these cases. Monitoring revealed no cariotoxic side effects. On the basis of our experience we are of the opinion that this method is devoid of clinical significance.

Selective Venous Blood Withdrawal and Radioimmunoassay for Parathyroid Hormone

Good results in the preoperative localization of parathyroid tumors have been obtained with selective venous blood sampling from the cervical and thyroid veins and determination of the parathyroid hormone concentration in the samples by radioimmunoassay.[3,9,23,24,27,28,30,34,38] To this end blood is taken from the venous plexus of the thyroid, the jugular vein, the brachiocephalic vein, and the superior vena cava through a catheter inserted into the femoral vein. This is done on both sides of the neck. The diagnostic value of this method, introduced by Reitz and associates,[27] has been impressively demonstrated of late. O'Riordan et al.[23] definitely localized the parathyroid tumors in 24 out of 29 patients who were examined by a large vein puncture. Other authors did not obtain good results with this method. Of late, blood sampling from small veins of the thyroid

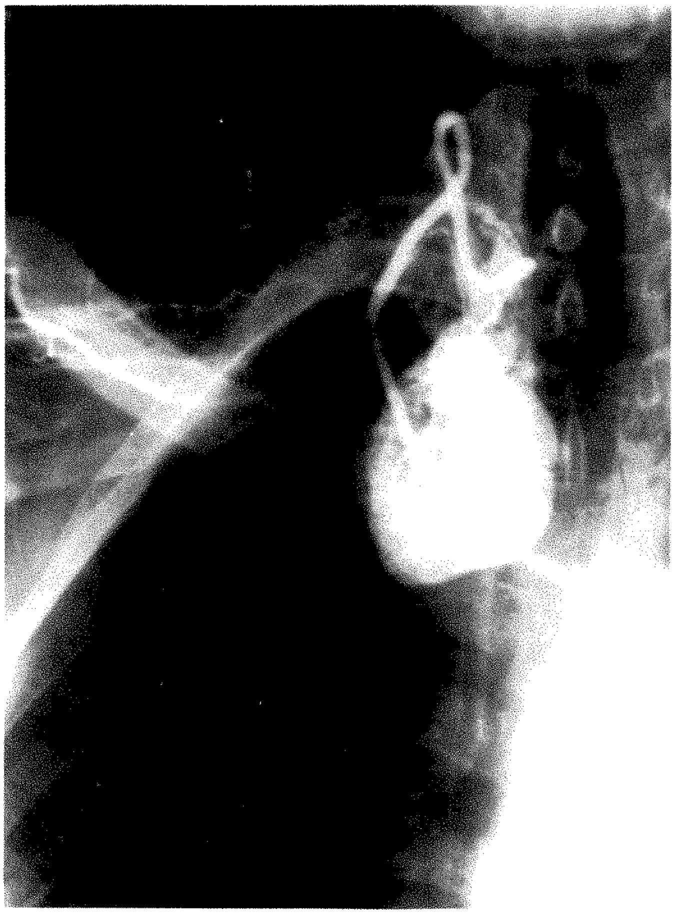


FIG. 3. (same case as Figs. 1 and 2): Selective angiography of the right inferior thyroid artery shows the tumor again. Now demonstration of two different tissues—one surrounding the other—is achieved. Microscopic examination after surgery reveals a struma aberrata vera with a centrally placed parathyroid tumor.

TABLE 4. *Localization Techniques Used in Primary Hyperparathyroidism*

	Positive	Negative	Doubtful	Total
Parathyroid scintiscans	4	14	3	21
Arteriography	7	8*	1	16
Pneumomediastinum	3	4	1	8
Toluidine blue method	—	5	1	6
Selective determination of parathyroid hormone	17	2	1	21

* Examination discontinued because of cerebral circulatory disturbances in one of these cases.

plexus, chiefly the two inferior thyroid veins and their branches, where the hormone is not yet diluted by blood from the head and upper thorax region, has proved its superiority. Small vein sampling, although requiring more time and being technically more difficult, in view of its improved results should be preferred to large vein sampling, if possible.[3,9,29,30,38] A simultaneous venogram of the thyroid and neck is indispensable because the strictly side-split drainage of the parathyroid blood, described by Doppmann and Hammond,[8] is not always present.[29,30,38] In patients with a solitary adenoma an unilateral concentration gradient of at least 2:1 is diagnostic. Bilaterally elevated values indicate the presence of several adenomas or hyperplasia. In the case of intramediastinal tumors, the values found in the brachiocephalic vein and the superior vena cava were elevated by comparison with the inferior thyroid vein. We for our part were able to confirm the presence of 17 out of 21 parathyroid adenomas by this method.

Operative Technique for One-Time Procedure

A typical Kocher neck incision is performed. Following exposure of the capsule the two halves of the thyroid are displaced. The posterior surface of the thyroid capsule is carefully scanned. Importance should be attached particularly to careful, bloodless preparation since hematomas in the loose connective tissue may conceal differences of color. Scanning of the posterior side of the thyroid, its lower and upper poles and of the thyroid compartments in the broadest sense will localize the majority of the parathyroid glands. If not, the larger environment of the thyroid, the perivascular sheaths of carotid artery and jugular vein, the paralaryngeal region, and the esophagotracheal sulcus (via careful handling of the recurrent laryngeal nerve) are examined. Particular attention must be paid to the course of the inferior thyroid artery since the area it supplies encompasses a large number of likewise ectopic parathyroids. If the search proves negative, a careful digital examination is made of the retrosternal connective tissue, notably on the left paratracheally as far as the aortic arch, and as far as the subclavian artery on the right. Excessive blunt exploration without visual control should be avoided. Even though in our own patients digital exploration caused no injury to mediastinal organs, we may call attention to the report by Nathaniels et al.[21] who described the development of a bilateral pneumothorax following uncontrolled exploration of the retrosternal space.

If this further exploration remains unsuccessful, the two halves of the thyroid are subtotally resected. The tissue thus removed is immediately cut into slices and searched for suspicious areas. The entire material is turned over to the pathologist for histologic processing.

If no parathyroid tumor has been found by this time, biopsy from a normally appearing parathyroid gland should be attempted in order to check on the possibility of hyperplasia.

If there is no hyperplasia, we do not—in contrast to most authors[5,21,26,31,32]—terminate the procedure at this point. The immediately ensuing sternotomy and exploration of the anterior mediastinum do represent a substantial extension of the intervention but in our estimation they are more justifiable than a second operation later on. The likelihood that the parathyroid tumor will be located in the anterior mediastinum is great. In only about 1–2% of patients is it situated in the posterior mediastinum and requires removal by thoracotomy. However, this requires comprehensive preoperative preparation of each patient with primary hyperparathyroidism that should make it possible to follow through with an intrathoracic operation without any delay.

Exploration extends primarily to the thymus and the surrounding mediastinal connective tissue. Even if a tumor is found in the anterior mediastinum outside the thymus gland, its removal is indicated because parathyroids are fairly often present in the glandular parenchyma. If no tumor is discovered, both the thymus and the surrounding adipose and connective tissue are extirpated and carefully prepared. Painstaking work-up of the material by the pathologist is indispensable.

By this procedure we succeeded in localizing 56 parathyroid tumors.

Discussion

When parathyroid tumors are multiple and ectopic, they are more difficult to find and to remove surgically. As methods of localization, we prefer arteriography, pneumomediastinum, and above all selective blood sampling and radioimmunologic determination of parathyroid hormone. However, we have been using this last technique for a short time only and have not yet applied it to a patient with a mediastinal tumor. We consider it inadvisable to perform a surgical exploration without use of a localization technique, though this has been recommended by some authors.[1,21,26,31,40]

In our opinion surgical exploration should include the anterior mediastinum in the same session if cervical examination has not uncovered a parathyroid tumor. We find that after careful exploration and conscientious hemostasis a second operation has become unnecessary provided rapid section examination of the numerous tissue specimens is assured. In view of improved anesthesiologic conditions and standardized operative techniques we believe that operation in two phases is superfluous.

Our favorable experience with all those patients in whom we performed cervical and mediastinal exploration in a single session (Cases 3, 5 and 7 in Table 3) has made us turn away from the two-phase procedure. The sternum is incised step by step. If the location of the mediastinal adenoma permits, partial sternotomy may suffice. In case total exploration of the anterior mediastinum is necessary, opening of the entire sternum is indispensable.

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Fresh and Cultured Thyroid Gland:

Survival and Function after Implantation

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Isogeneic or allogeneic thyroid glands were implanted into thyroidectomized recipient rats. These grafts, either fresh or cultured, were placed in hamstring muscle pocket or under the renal capsule. Survival and function of the grafts were evaluated by: restoration of normal levels of serum thyroxine, weight gain, kidney transamidinase (a thyroxine-induced enzyme), and histological appearance of re-excised implants. All isografts, fresh and cultured, functioned well as ectopic thyroid glands, though restoration of normal serum thyroxine levels was more rapid for the fresh implants. Fresh allografts functioned transiently but then failed due to rejection. No function was detected for cultured allografts, and rejection was seen histologically. The rat thyroid allograft therefore differs from the rat parathyroid allograft, which often can function for several months despite histological evidence of rejection. Maintenance in tissue culture prior to implantation does not appear to alter the long-term immunogenicity of either organ.

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THE IMPLANTATION of endocrine tissue grafts is likely eventually to become clinically useful for correcting hormonal deficiencies. While patients with endocrine deficiencies such as hypothyroidism, hypoparathyroidism, and diabetes mellitus are now "adequately" managed by appropriate daily replacement therapy, the absence of a physiologic autoregulatory mechanism, particularly in the case of diabetes, can lead to life-threatening emergencies.

The only, though formidable deterrent to allografting or xenografting endocrine tissue is immunologic rejection. Histological and functional evidence has been obtained that rejection of endocrine tissue occurs for all tissues tested, including parathyroid,[30,31] thyroid,[8,33] adrenal,[26] ovary,[12,25] and pancreatic islet.[1] In the human, all cells studied so far except red blood corpuscles bear HL-A histocompatibility antigens on their surfaces.[4]

In the past, endocrine tissue, and particularly thyroid, has been thought to be less immunogenic than other tissue. This belief was based on work by many investigators over the past century, mainly in rodents and rabbits, which has been extensively reviewed by Woodruff[14] and by Brooks.[7] Many of the early reports were concerned with demonstrating the possible advantages of various transplantation sites, of thyroid deficiency in the recipient ("the Halsted principle"), and of the use of fetal tissue. Optimism was generated by the report of Woodruff and Woodruff,[45] who showed that thyroid allografts which had been "adapted" for 6 to 10 months in the anterior chamber of the host's eye were subsequently accepted if retransplanted subcutaneously. More recent work in rats by Warden, Reemtsma and Steinmuller,[40] using serum thyroxine levels as a test for graft viability, has verified the Woodruffs' observation, though their evidence indicates the host adapts to the grafts, not the graft to the host.

In contrast to these reported successes with endocrine transplantation in small laboratory animals, allotransplantation of parathyroid and thyroid in the dog by Halsted,[14] Longmire,[33] Fisher,[8] Wells[42] and their associates has resulted in rejection, unless the recipient was immunosuppressed.

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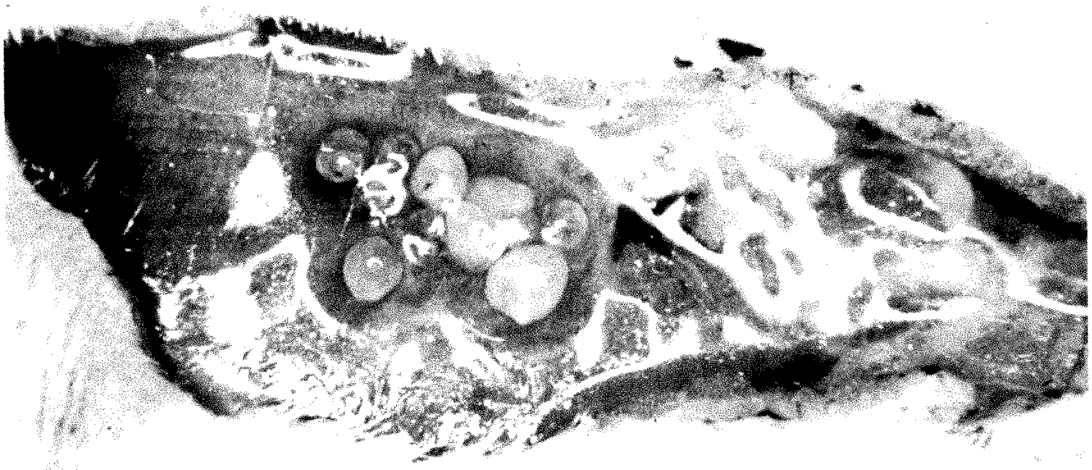

FIG. 1. Method of thyroid implantation into a hamstring muscle pocket. The thyroid lobe to be transplanted was minced and maintained in tissue culture for 14 days. An incision 1.8 cm long was made in the skin overlying the left hamstring muscles of the thyroidectomized host rat. The cultured thyroid fragments were laid (as shown) on the deep fascia, which was also incised. All fragments were inserted into a pocket developed in the underlying muscle, and the fascial incision was closed with a single silk stitch.

Further optimism regarding decreased immunogenicity of endocrine tissue came from the many reports of successful endocrine transplantation in humans, especially of the parathyroid, which have appeared over the past one hundred years. The recent review of human parathyroid transplantation by Jacob and Dunphy[15] shows that "successful" results were invariably based on symptomatic relief rather than on histological evidence of graft survival. Special techniques thought to contribute to success included the "conditioning" of grafts in tissue culture prior to implantation,[36] the use of cultured fetal tissue,[9] and the rapid transfer of fresh tissue from donor to recipient—in one case from a guillotined criminal![44] Further confusion was introduced when it was found that clinical improvement (e.g. less frequent episodes of tetany), could occur following endocrine allografts despite histologic evidence of graft rejection.[32,41] Possible explanations for this have been discussed by Jordan,[18] who though lacking histological evidence claimed to have 6 patients with improvement for longer than 1 year after parathyroid allograft transplantation.

Excellent evidence for the survival and function of human parathyroid autografts has recently been presented by Wells.[43] He and his associates have performed intramuscular forearm autografts into 28 patients following total parathyroidectomy for secondary or primary hyperparathyroidism. Function of the implants was proved by biopsy and by demonstration of elevated parathyroid hormone levels in antecubital venous blood draining the grafted tissue. Two cases of acceptance of parathyroid allografts in immunosuppressed (renal allografted) humans, proved by biopsy, have also been reported.[13,43]

The use of genetically well defined strains of experimental animals will, we hope, permit clarification of this controversial field. In 1959, for example, Russell and Gittes[31] reported that parathyroid allografts between partially inbred strains of rats sometimes survived for long intervals. Histological and functional (maintenance of normocalcemia) evidence of survival was presented. We[30] have recently extended and confirmed the work of Russell and Gittes by transplanting parathyroid allografts between two highly inbred strains of rats (Brown Norway and Wistar Furth) which have a major histocompatibility difference at the Ag-B locus (Ag-B^3 versus Ag-B^2, respectively), analogous to the HL-A locus in man. While all isogeneic parathyroid implants survived indefinitely, about one-third of the allogeneic grafts functioned longer than 30 days despite histological evidence of concurrent rejection. Thus, in the case of the rat parathyroid, a deficiency of transplantation antigens may exist.

The maintenance of both parathyroid and thyroid in tissue culture has reached high levels of sophistication in the hands of Sherwood and Kerkof, respectively. Sherwood,[34] studying parathyroid hormone (PTH) production from organ cultures of bovine and human parathyroid, found that these cultures remain histologically intact for more than 2 weeks and continuously release PTH into the culture medium. The rate of hormone release is reciprocally related to the divalent cation (Ca plus Mg) concentration.

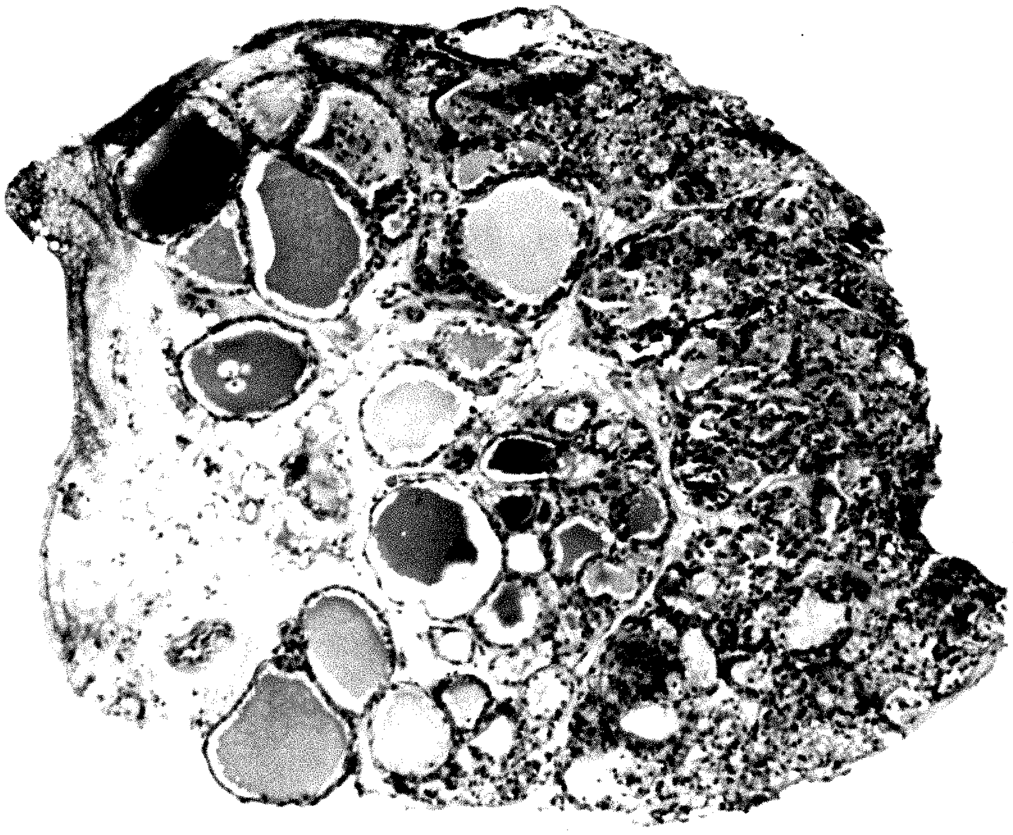

FIG. 2a. Section of fresh BN thyroid (×125).

Kerkof has demonstrated that monolayers of sheep thyroid cells in tissue culture will reorganize into a follicular pattern in the presence of thyroid stimulating hormone (TSH).[20] ^{131}I uptake and incorporation into iodoamino acids was also enhanced.[21] Rat thyroid cells maintained in culture for 3 days were shown to reorganize into follicles when reimplanted subcutaneously into thyroidectomized recipient rats of the same strain.[22] The reorganized follicles functioned, incorporating ^{131}I into iodoamino acids and releasing ^{131}I-thyroxine into the circulation.

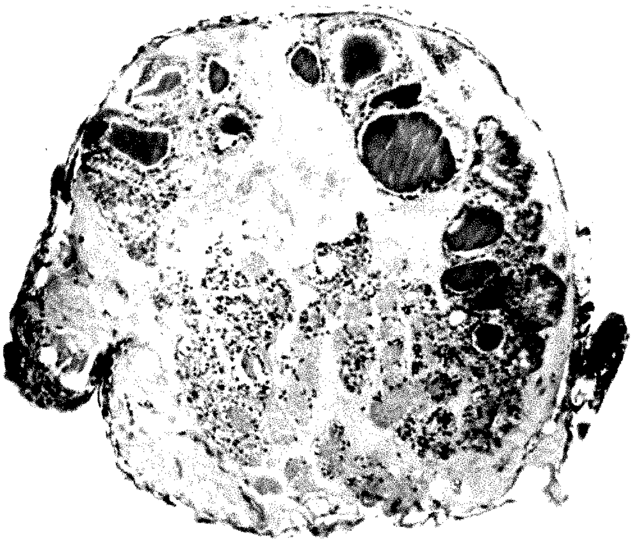

FIG. 2b. Section of fragment of BN thyroid which has been maintained in tissue culture for 22 days. A significant number of follicles appear intact (×87.5).

Because of recent reports that prior maintenance in culture of mouse tumor[16] and skin[37] allografts leads to their increased survival after transplantation, we compared survival of fresh and cultured rat parathyroid implants.[30] Our cultured parathyroid isografts invariably survived, while no survival advantage was seen in the cultured versus fresh allografts. The present report concerns further experiments using the rat thyroid, with animals of the same genetic background as were used in the parathyroid studies. A comparison of the immunogenicity of these two tissues was then made. The effect of prior culture on the survival of rat thyroid isografts and allografts was also examined.

Materials and Methods

Animals: 35 weanling Wistar Furth (WF) male rats purchased from Microbiological Associates, Ambler, Pa., were surgically thyroidectomized at 4 weeks of age by the Hormone Assay Laboratories, Chicago, Ill. In

TABLE 1.

SERUM THYROXINE IODIDE AFTER THYROID TRANSPLANTATION

A. Controls	No. animals per group	micrograms/100ml. serum		
1. Intact, not grafted	5	2.42 ± 0.14		
2. Thyroidectomized	5	0		
B. Throidectomized & thyroid graft implanted		micrograms/100ml. serum after implant in place for:		
		1wk.	4 wks.	3–4 mos.
1. Fresh isograft	5	3.12 ± 0.41	2.16 ± 0.16	2.20 ± 0.31
2. Cultured isograft	5	0.60 ± 0.60	1.66 ± 0.18	1.86 ± 0.17
3. Fresh allograft	8	2.00 ± 0.50	0.09 ± 0.04	0.24 ± 0.11
4. Cultured allograft	7	0	0	0.22 ± 0.09

order to ablate any residual or ectopic thyroid tissue, 5 μC of ^{131}I per gm body weight was then injected intraperitoneally on the second day after surgery. The rats were maintained on a synthetic thyroxine-free diet and on tap water to which 0.3% calcium lactate had been added. The diet consisted of casein and corn oil supplemented with vitamins and minerals. Lack of weight gain over a 5 week observation period prior to thyroid transplantation (at 2–3 months of age) was used as an indication of complete thyroidectomy. Four animals were removed from the experimental group on the basis of inadequate weight stability. An additional 10 WF weanling rats were obtained to be used as intact controls and as donors of isogeneic thyroid. Adult Brown Norway (BN) rats from the colony of the Sloan-Kettering Institute were employed as allogeneic thyroid donors. The weights of all rats were recorded each week for the duration of the experiment, and the weight data were used as a parameter of thyroid graft function.

Preparation and implantation of thyroid grafts: Thyroid glands used for implantation were removed by microsurgical techniques from isogeneic (WF) or allogeneic (BN) donors. Each lobe was removed separately and divided into 6 to 8 pieces measuring less than 1 mm in diameter. If the lobe was to be cultured, the pieces were fixed by a thrombin-fibrinogen clot to a sterile cover slip, which was in turn immersed in a petri dish containing Eagle's minimal essential medium with Earle's salts (GIBCO), 10% calf serum, 2mM L-Glutamine, penicillin (100 units/ml), streptomycin (100 μg/ml), and amphotericin B (0.25 μg/ml). In a few dishes thyroid stimulating hormone (Thytropar*) at a concentration of 0.17 unit/ml was added. Incubation was at 37 C in 5% CO_2 in air and 100% humidity.

Implantation of fragments of thyroid into a left hamstring muscle pocket was performed as shown in Fig. 1. The recipient animals were anesthetized with intraperitoneal injection of chloral hydrate, 1 cc per gm body weight of a 3.5% solution. Through a 1 cm skin incision in the lateral thigh an opening was made in the fascia, and a pocket about 5 mm deep in the muscle was developed by spreading with fine, pointed, bayonet-handled scissors. Hemorrhage was avoided. The fragments of thyroid were gently inserted into the pocket, which was closed with a single black silk 6-0 suture marking the implantation site to facilitate future biopsy. The skin was closed with metal clips.

The technique of implantation beneath the renal capsule was similar. The left kidney was exposed through a flank incision, and the thyroid fragments placed on the surface of the kidney capsule. Through a 1 mm incision in the capsule (avoiding the parenchyma, which bleeds profusely if damaged) the implants were teased underneath and distributed evenly over the renal surface.

Both methods of implantation were easily accomplished with the aid of a dissecting microscope and microsurgical instruments. The renal capsule offered the advantage that if rejection occurred, the implantation site could be recognized later and biopsied due to the development of an easily visualized area of fibrosis at the site of rejection.

Thyroxine assay: Each animal was bled from the tail vein at intervals, and the thyroxine iodide in the collected serum (which includes both T_4 and T_3) was measured by the Bio-Rad† column method.

Kidney transamidinase assay: Three to 4 months after thyroid implantation all animals including intact and thyroidectomized non-implanted controls were sacrificed. Biopsies were performed of all left renal or hamstring muscle implants and the right kidney of each animal was assayed for the enzyme transamidinase by a method previously described by Van Pilsum et al.[38] Since the

TABLE 2.

WEIGHT GAIN

(first 13 weeks after thyroid transplant)

A. Controls	grams
1. Intact, ungrafted	179.8 ± 8.5
2. Thyroidectomized	45.6 ± 8.6
B. Thyroidectomized, and thyroid graft implanted	
1. Fresh isograft	160.2 ± 7.6
2. Cultured isograft	139.6 ± 5.4
3. Fresh allograft	62.9 ± 6.5
4. Cultured allograft	32.4 ± 5.9

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* Bovine TSH; Armour Pharmaceutical Co., Kankakee, Ill.

† Bio-Rad Laboratories, Richmond, California.

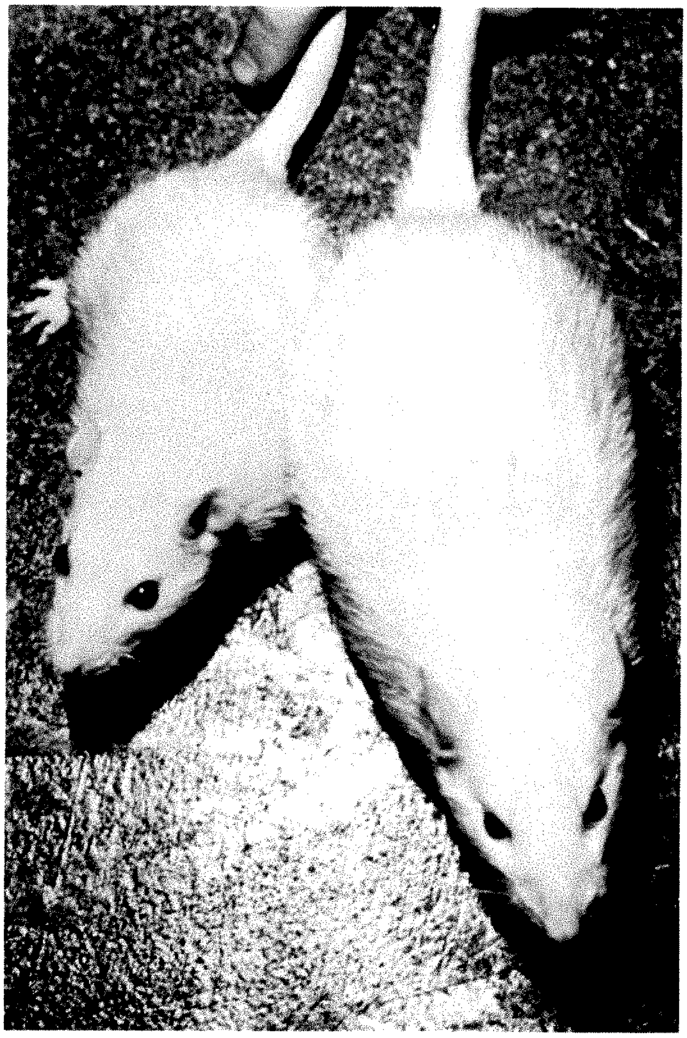

FIG. 3. Thyroidectomized, littermate WF male rats. The rat on the left is a thyroidectomized control animal and weighs 120 gm. The one on the right received a fresh thyroid lobe isograft 12 weeks previously, and now weighs 250 gm.

enzyme is induced in young rats by thyroxine, it was useful as another measure of thyroid implant function.

Results

Maintenance of thyroid in tissue culture: Six to 8 fragments from one thyroid lobe, each measuring less than 1 mm in diameter, were explanted into a petri dish and were maintained in culture for up to 14 weeks. Grossly, we noted a tendency for the fragments to assume a spherical shape and for fibroblasts to grow out from the explants over the plastic surface of the tissue culture dish. Microscopically, these fibroblasts were seen to encapsulate the explants after about the fourth day in culture, a phenomenon which we had observed previously for rat parathyroid explants and which has been described for cultured fragments of human prostate (M. M. Webber: personal communication).

Histologic examination of cultured thyroid (Fig. 2) demonstrated surprising survival of follicular structure after 2 to 3 weeks and a few viable appearing follicles even after 14 weeks of culture. Microscopic central necrosis was common, with the most viable appearing tissue being at the periphery. This was undoubtedly due to better diffusion of nutrients at the edges. No consistent difference in the appearance of cultured fragments was noted when TSH was included in the culture medium. Fragments used for grafting were maintained in culture for 2 weeks.

Functional measurements of thyroid implant survival: The thyroidectomized recipient (WF) rats were divided into groups of 5 to 8, and each group designated to receive isografts or allografts, either fresh or cultured (Table 1). Control groups of 5 thyroidectomized and 5 intact, ungrafted animals were also maintained. Three different functional parameters were used to evaluate thyroid implant survival: serum thyroxine, weight gain and the level of a thyroxine-induced kidney enzyme, transamidinase. Data are presented as the mean plus or minus the standard error.

Results of the serum thyroxine determinations are presented in Table 1. Values were obtained at several times (including the beginning and end of the experiment) for the 2 control groups. A mean of 2.42 $\mu g\%$ was found for intact animals, and all animals in the thyroidectomized control group consistently had undetectable levels of serum thyroxine. No spontaneous recovery of thyroid function was found in the thyroidectomized controls. Restoration of normal serum thyroxine levels occurred in recipients of fresh isografts within the first week after implantation and was maintained. Cultured isografts also restored normal levels of serum thyroxine, though full recovery did not occur for 3 to 4 months. Neither fresh nor cultured allografts functioned after 4 weeks. The normal serum thyroxine levels noted in recipients of fresh allografts at 1 week were probably due to temporary function prior to rejection, or could have been due in part to thyroxine released shortly after implantation, since the half life of plasma thyroxine (in humans) is 6.7 days. At the time of implantation the recipient thyroidectomized rats were 7 weeks old and weighed 90–100 grams. During the next 13 weeks the intact, ungrafted control animals gained a mean of 179.8 grams (Table 2) to achieve close to their full adult weight. Thyroidectomized control animals gained a mean of 45.6 grams. This was an obvious and statistically significant difference in weight gain between groups receiving isografts (Fig. 3) versus those receiving allografts, again indicating function in the former group and non-function in the latter. Weight curves of animals receiving fresh allografts showed a brief increment in growth following implantation consistent with temporary function.

Measurements of kidney transamidinase in all animals at the completion of these studies (Table 3) were consistent with the thyroxine and weight gain data. The kidneys from animals receiving either fresh or cultured isografts had fully induced levels of this enzyme, while allografted animals were deficient.

Approximately half of each experimental group received muscle pocket implants while the other half received renal capsule implants. By none of the parameters described above were any statistically significant differences found between the two implantation sites in any of the groups.

Histological examination of biopsied implants: Biopsies of implanted thyroid were performed at 1 week and 1 month for a few animals in each group, and an attempt was made to re-excise the implants from all animals at the completion of the studies. In the case of both fresh and cultured isografts, all implants were recovered, and viable appearing thyroid tissue was always found (Fig. 4). Both fresh and cultured allografts were heavily infiltrated with lymphocytes at 1 week following implantation. At 3 to 4 months the muscle pocket allografts could not be found, while the renal capsule allografts were seen histologically to have been replaced by fibrosis (Fig. 5).

Since the central necrosis was never seen during histological examination of thyroid isografts, we assume removal of non-viable material rapidly occurs following implantation and vascularization. It is likely that remodeling and regeneration of grafts take place.

TABLE 3.
KIDNEY TRANSAMIDINASE LEVELS
(3 to 4 months after thyroid transplant)

	u moles ornithine/ gm kidney/hr
A. Controls	
1. Intact, ungrafted	24.4 ± 2.5
2. Thyroidectomized	15.4 ± 2.4
B. Thyroidectomized, and thyroid graft implanted	
1. Fresh isograft	34.5 ± 1.8
2. Cultured isograft	32.2 ± 1.6
3. Fresh allograft	15.2 ± 2.2
4. Cultured allograft	11.6 ± 1.3

Discussion

Whether endocrine tissue allografts can be accepted without immunosuppression of the host under special circumstances continues to be a controversial issue. The studies presented here indicate that, using the BN-WF combination, rat thyroid allografts are rapidly and invariably rejected. We did not detect any alteration of immunogenicity by maintaining the grafts in tissue culture prior to implantation. Recently Lafferty and associates,[23] using ^{125}I uptake as a measure of graft survival, obtained data indicating an improved survival during the first three weeks following implantation of rat thyroid allografts after culturing for 12 days. They propose that this effect is due

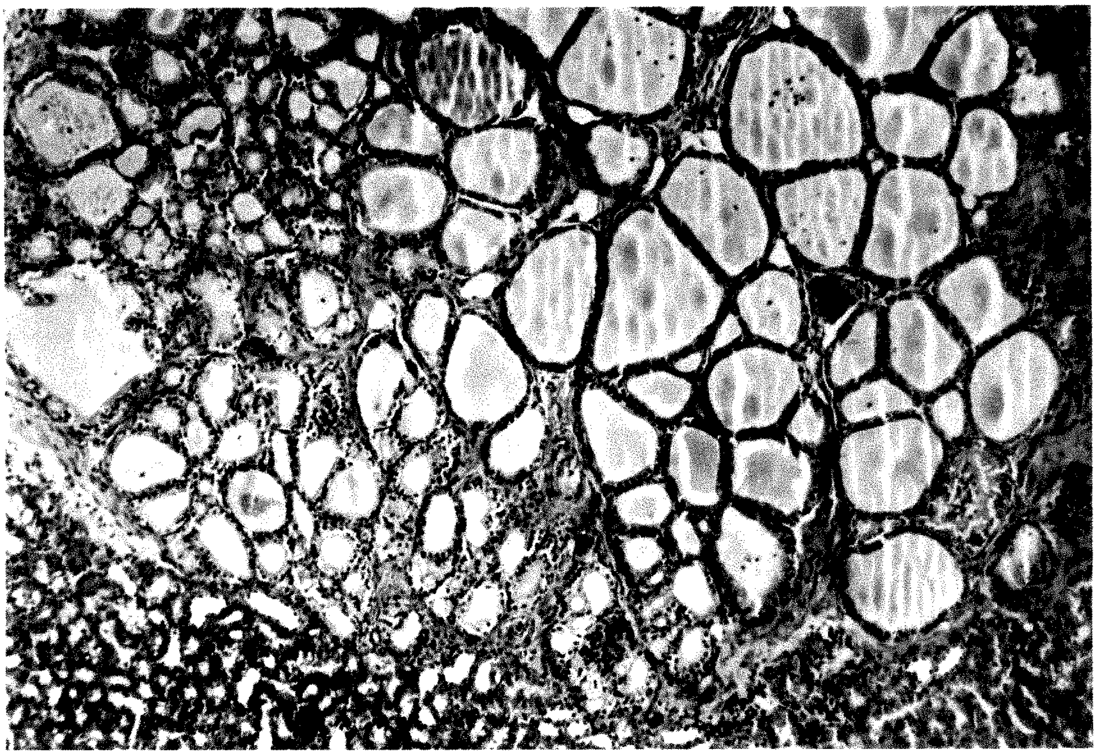

FIG. 4a. Histology of functioning thyroid isograft under the host renal capsule. Fresh isograft implanted 12 days before biopsy (×107.5).

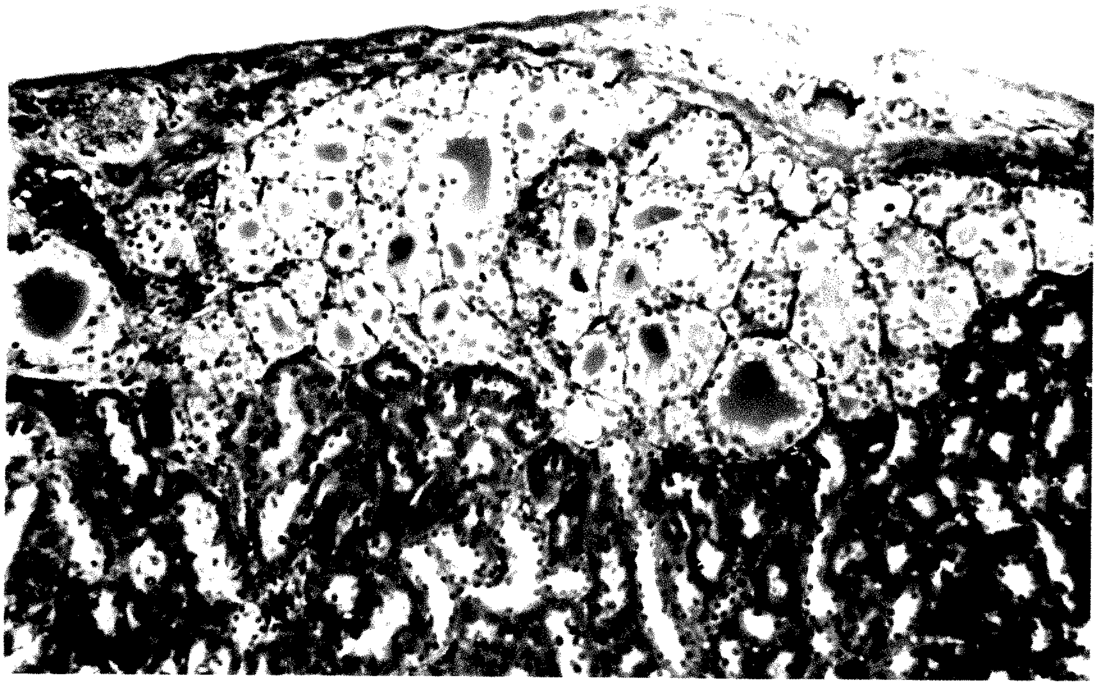

FIG. 4b. Fresh isograft implanted 3 months before biopsy (× 172).

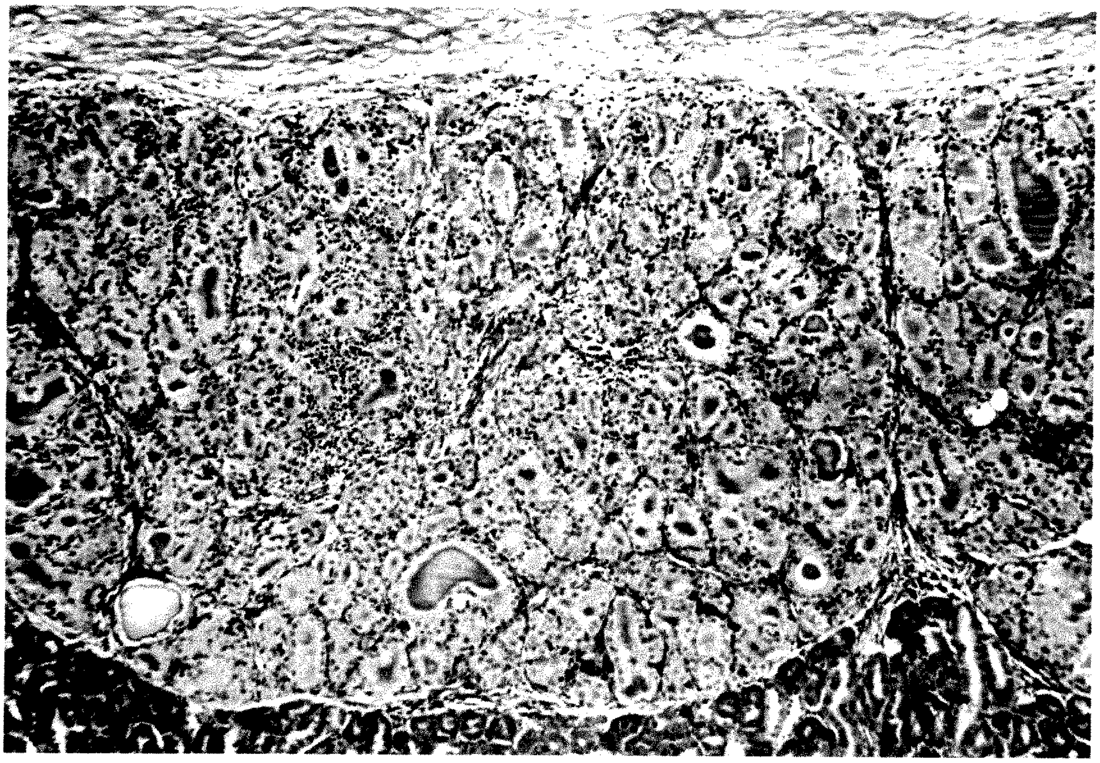

FIG. 4c. Isograft cultured 14 days, then implanted 3 months before biopsy (× 102.5). All isografts have intact follicular structure and appear viable.

to the loss of (sensitizing) passenger leukocytes during culture. Histologically, their implanted cultured grafts were infiltrated with lymphocytes. Such an early effect was not detected by our studies, since no measurable serum thyroxine was found at either 1 or 4 weeks following implantation of cultured thyroid allografts.

Reports of acceptance of mouse and human skin allografts following tissue culture[37] led to attempts by many

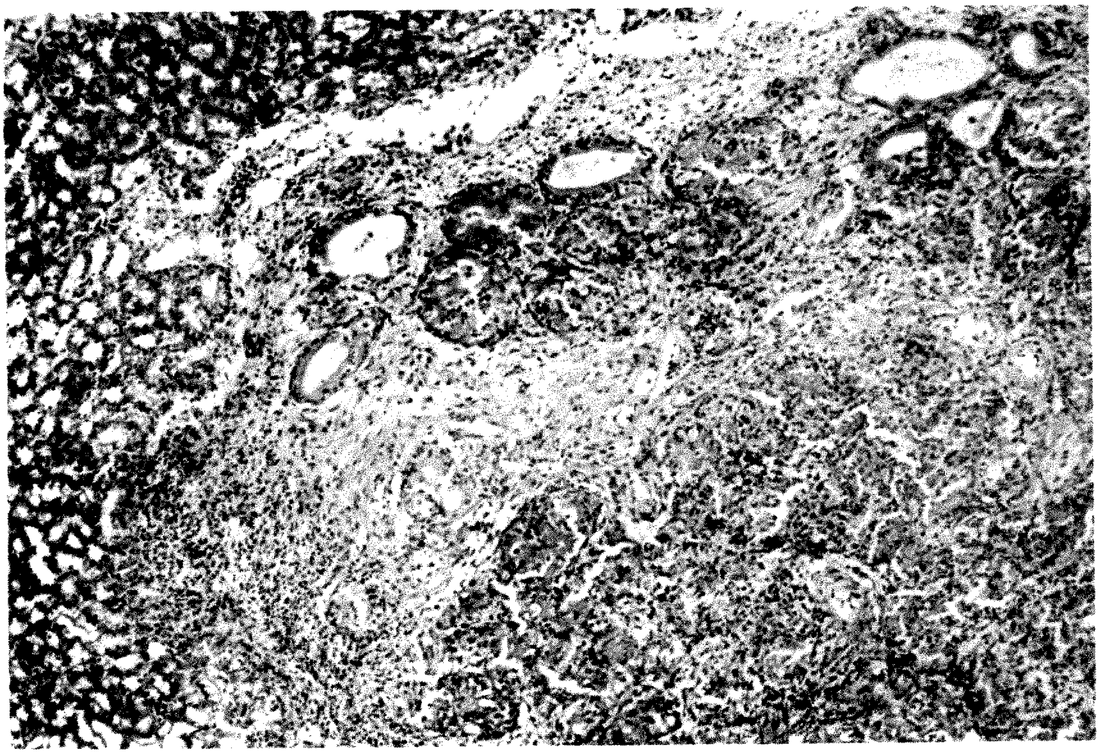

FIG. 5a. Histology of thyroid allograft under the host renal capsule. Fresh allograft implanted 10 days before biopsy (× 107.5).

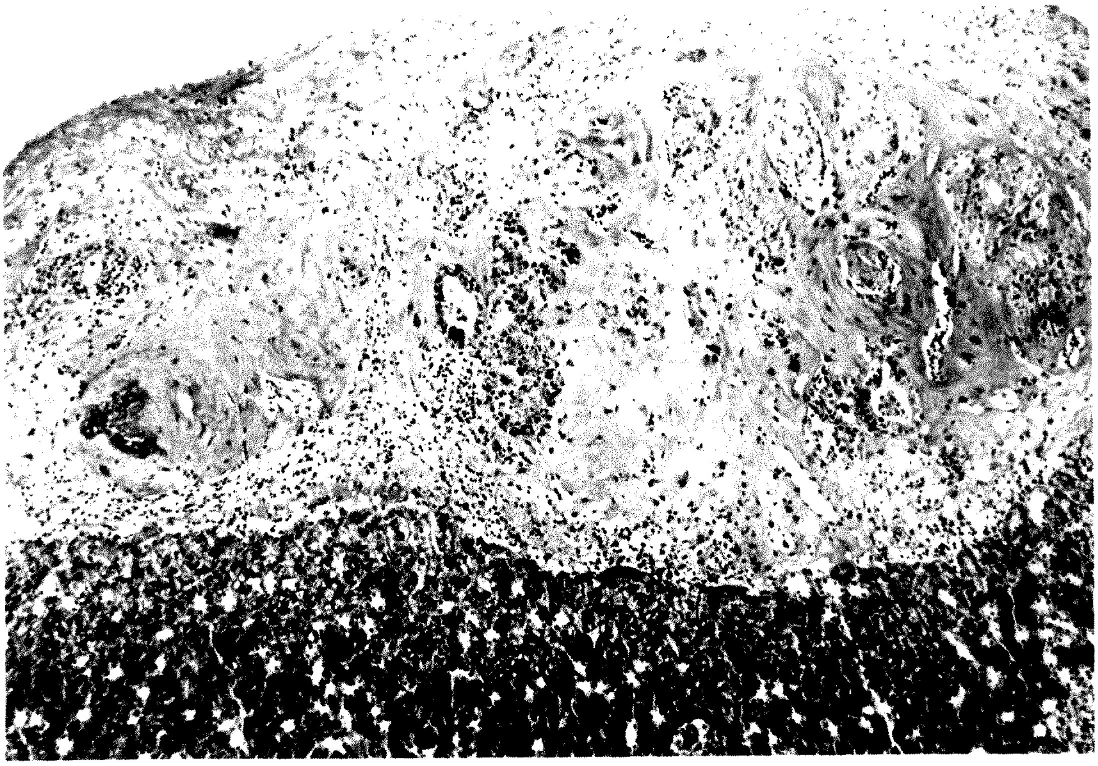

FIG. 5b. Allograft cultured 14 days, then implanted 35 days before biopsy (× 107).

others to reproduce these results. These attempts were not successful, and a study in the mouse by Ninnemann,[27] using many techniques of transplantation and donor-recipient combinations, showed that prior culture did not prolong mouse skin allograft survival. A later study has shown that even immunogenicity due to the weak H-Y histocompatibility antigen is not altered by skin graft culture.[39] Thus cultured male mouse skin is capable of

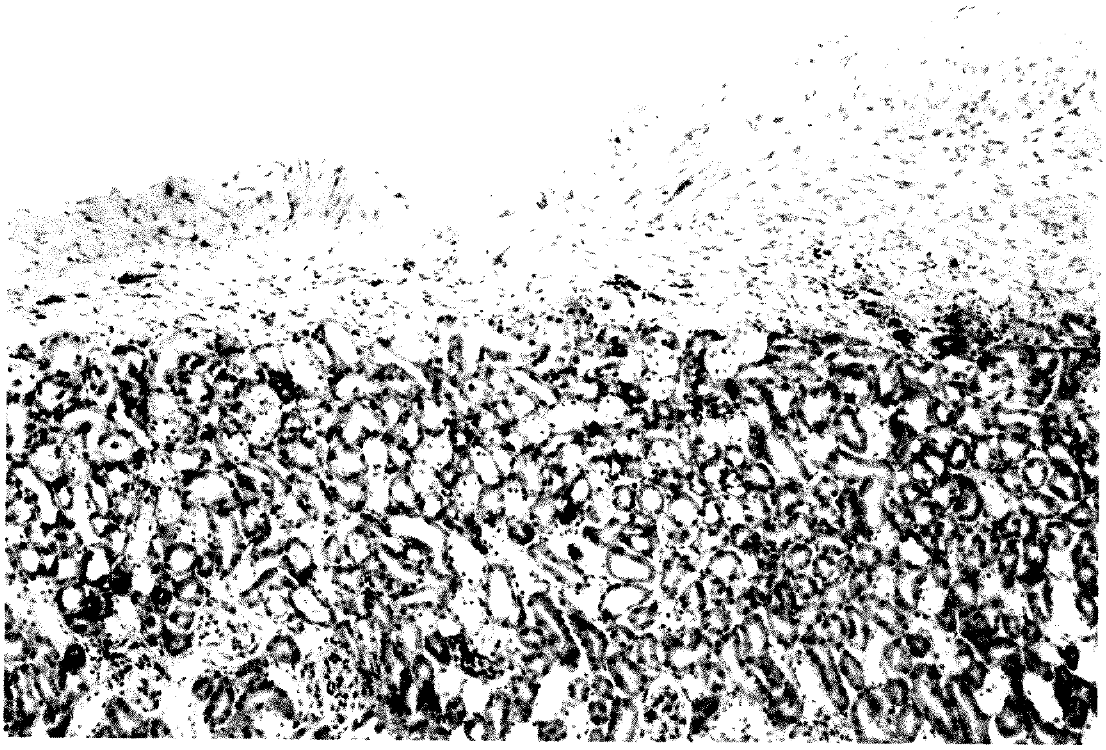

FIG. 5c. Fresh allograft implanted 3 months before biopsy (×137.5). All allografts are infiltrated with lymphocytes and are undergoing rejection. By 3 months following implantation only fibrosis remains.

sensitizing a female recipient so that a second uncultured male graft will undergo a second set rejection.

Jacobs[16] has performed careful work showing that a murine (BALB/c) Leydig cell tumor can be made transplantable into a DBA/1 mouse, thus crossing the H-2^d to H-2^q histocompatibility barrier, by prior culture for 6 to 28 days. The exact mechanism of this change is not known. Ninnemann has confirmed these results, and found that culturing the tumor does not permit it to be accepted by murine recipients of other H-2 types.[28] He found that homogenizing the tissue rather than culturing it permits acceptance. Linder[25] demonstrated that certain mouse tumors (and to a lesser extent, mouse ovaries) can transgress weak (non-H-2) histocompatibility differences, while skin grafts are uniformly rejected. Also, he showed that mice which accept allogeneic ovaries often subsequently accept a skin graft from the same donor. Two reports that maintenance of mouse ovary in culture decreases its immunogenicity have recently appeared, Jacobs[17] again exploring the BALB/c-DBA/1 combination, and Leuker and Sharpton[24] using outbred mice. Further work with other inbred strains is needed.

Efforts are in progress by many groups to overcome the technical problems of isolating and transplanting pancreatic islets, a difficult endeavor due to the close association of islets with pancreatic exocrine tissue. Isografts have been reported to have successfully functioned in rats[1] and mice,[29] though late failure of pancreatic islet isografts, not seen with thyroid and parathyroid isografts, has been reported.[11] Unfortunately islet allografts, even if cultured[11] or derived from fetal tissue (C. Barker: personal communication), appear to be highly immunogenic and are rapidly rejected. Nonetheless, much useful information regarding islet function and the pathogenesis of diabetes is likely to be gained from animals bearing pancreatic islet isografts.

Our own studies and those of Russell and Gittes[31] indicate that in the rat, the parathyroid may be only weakly immunogenic. We showed[30] that in the BN-WF donor-host combination, 10 out of 35 (29%) of the allografts survived and maintained normocalcemia for greater than 30 days, considerably longer than expected on the basis of the usual rejection time for BN to WF skin grafts (9–11 days). Very minimal lymphocytic infiltration is seen histologically in such a slowly rejecting parathyroid allograft (Fig. 6).

Rat parathyroid and thyroid isografts are easily performed, and technical failures did not occur in our experience. The renal capsule and hamstring muscle pocket sites appear equally satisfactory, in agreement with the studies by Braunwald and Hufnagel[6] showing that a variety of sites were equally satisfactory for the survival of rabbit thyroid autografts. In the case of allografts, we thought that the muscle pocket might offer some protection against rejection, since studies by Barker and Billingham[2] indicated that it is a relatively privileged site. No advantage was apparent in our studies, however. The site of implantation may be more critical to the survival and function of the pancreatic islet, for which some investigators have found the portal vein to be superior to

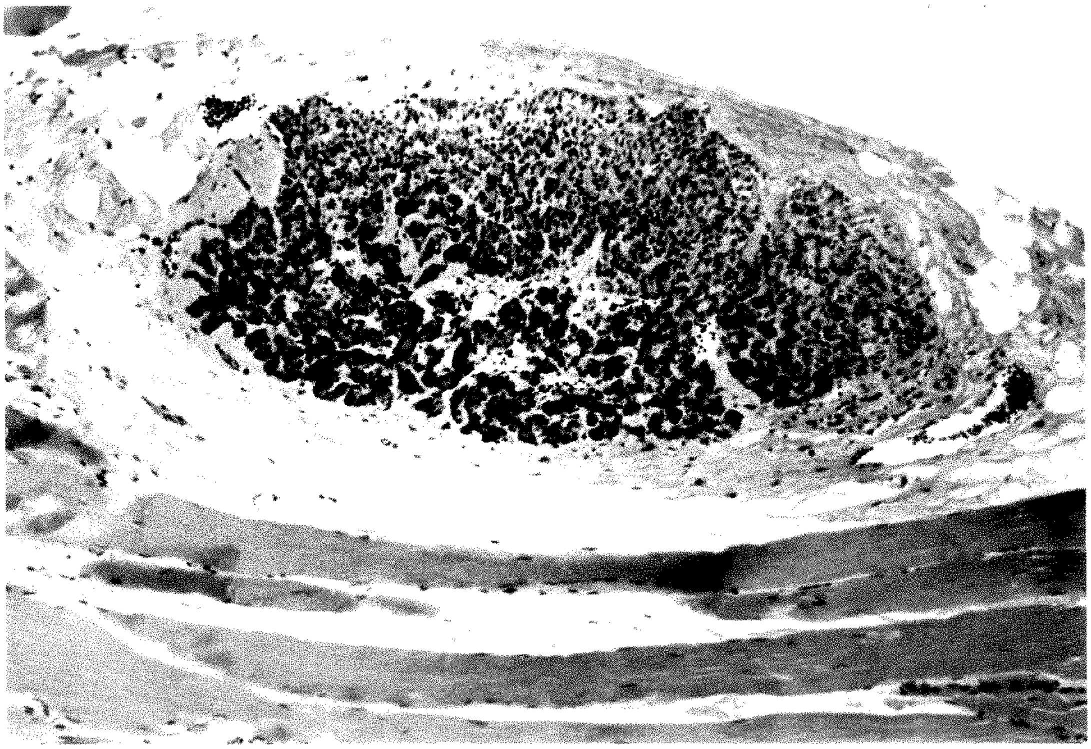

FIG. 6. Section of a fresh BN parathyroid allograft which survived as a muscle pocket implant in a parathyroidectomized WF recipient for 11 months. By 8 days after implantation of a single parathyroid the serum calcium had risen from 5.3 to 9.3 mg%. The animal remained normocalcemic thereafter even when challenged by a low calcium diet. The serum calcium at the time of biopsy was again 9.3 mg%. This is an example of function by a rat parathyroid allograft despite ongoing rejection, as evidenced histologically by a mild lymphocytic infiltrate (×142.5).

intraperitoneal injection.[19] Intramuscular implantation of islets has apparently been found less suitable but may deserve further study due to the potential convenience for clinical application. The most appropriate implantation site for a tissue may depend in part on whether its normal venous drainage is into the portal system. It is well to remember the experiments of Biskind and Biskind[5] which showed that ovarian tissue autotransplanted to the spleen in castrated female rats develops granulosa cell tumors, probably due to catabolism of estrogens in the liver and consequent release of pituitary hormones. So far we have not noted any tumors developing in either parathyroid or thyroid implants, and we are not aware that any have been reported.

We have found that the amount of rat parathyroid or thyroid implanted tissue required to achieve adequate hormone production is not critical, and that as little as one parathyroid or one thyroid lobe can lead to normocalcemia or a physiologic serum thyroxine level, respectively. We have not observed hypercalcemia or abnormally high levels of thyroxine in host animals, though Gittes reported he was able to make a recipient mildly hypercalcemic by implanting 40 parathyroid glands into a single rat.[10] Apparently, if an adequate amount of either tissue is implanted, the biochemical feedback mechanisms of cells in even cultured implants will operate to maintain normal hormonal levels. Quantitative requirements for pancreatic islets appear more stringent.

Our studies using BN rats as donors and WF rats as non-immunosuppressed recipients indicate that the thyroid allograft is invariably rejected, while the parathyroid allograft may survive and function for many months. A difference in immunogenicity between these two tissues therefore appears to exist. It is likely that various tissues differ in the amount of histocompatibility antigen which their cell surfaces bear,[3] the most striking example being the trophoblast which appears totally to lack immunogenicity.[35] Whether histocompatibility antigen is actually missing from trophoblast membrane or is effectively masked (by enhancing antibody?) is not known.

We do not know why some rat parathyroid implants survive long periods, while others undergo a more rapid form of rejection with a mean duration of function of only 17 days.[30] It may be significant that parathyroid isograft implants, on biopsy, are always surrounded by a small amount of thyroid which is inevitably explanted with it from the donor. On the other hand, functioning (but slowly rejecting) parathyroid allografts are rarely seen to be accompanied by thyroid, which may be presumed to have been rejected. Perhaps the amount of the more highly immunogenic thyroid inadvertently implanted with the parathyroid determines the degree and nature of the host's rejection response.

Routine clinical application of endocrine allografts awaits further understanding and control of rejection. An effective method to alter the immunogenicity of allografts may eventually be found. More specific or less hazardous methods of immunosuppression also may be discovered, though conventional immunosuppression in humans to avoid rejection of parathyroid or thyroid allografts seems not to be justified at present, except when the patient is already the recipient of a renal allograft. We believe that further progress in the area of experimental endocrine tissue transplantation is now possible. Future studies in animals should be based on the use of genetically defined inbred strains. Direct measurement both in animals and man of hormones produced by endocrine grafts, as well as histologic examination of re-excised implants, must be performed to avoid difficulties in deciding whether grafts have functioned or survived.

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Lumbar Sympathectomy in End Stage Arterial Occlusive Disease

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Sixty-one patients had lumbar sympathectomies performed for end stage occlusive vascular disease manifested by gangrene of less than one-half of the foot, ulcerating ischemic lesions, rest pain or rapidly progressive markedly limiting intermittent claudication. The operative procedure was standardized to permit removal of the lowermost preganglionic fiber at the level of the crus of the diaphragm and the ganglionated chain to the crossing of the iliac vessels. The immediate postoperative mortality was 6.5% from cardiac causes. Over all improvement rate was 60% while early amputation rate was 40% for the entire group. Those patients with rest pain had the poorest prognosis with an amputation rate of 53%.

The results are compared to other groups and factors of patient selection, anatomy of the sympathetic chain in relation to operative technique, physiology of decentralization versus denervation are discussed. The procedure is worthwhile in patients who are not candidates for arterial reconstruction who are faced with the prospect of early amputation.

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SINCE ITS INTRODUCTION approximately 50 years ago by Adson and Brown,[1,5] lumbar sympathectomy has engendered considerable controversy. Originally introduced for the relief of vaso-spastic disorders, Smithwick and Atlas successfully employed it in the treatment of occlusive arterial disease as well.[2,12] As they apply to occlusive arterial disease, the controversies in part are due to differences in patient selection so that many series are not comparable to each other due to the widely different stages of occlusive disease included.[9,13] Indeed, some also report its effect on the patency rates of arterial reconstructions. In part, they may be due to differences in criteria for success. In some measure they may be due to differences in surgical technique.[9,14]

The present series is reported since it is made up of an easily defined population group of patients with end stage inoperable arterial disease of the lower extremities. These patients usually had either rest pain or ischemic lesions. Only a few had severely limiting rapidly progressing intermittent claudication. All patients had angiographic studies and their arterial occlusions were considered to be inoperable by criteria previously outlined[8] in that there was no portion of any tibial artery in communication with a pedal arch in the presence of either femoral, popliteal or tibial arterial occlusions. The surgical technique was standardized and was easily duplicated in successive cases.

Materials

Sixty-one lumbar sympathectomies were performed by the authors on 58 patients from January, 1970 to December, 1974 for lower extremity arterial occlusive disease at the New York University Hospital. The follow up period was from 6 months to 4 and one half years. Four lumbar sympathectomies were performed in association with vascular reconstructions, of which 4 were excluded from this report.

Two categories of occlusive vascular disease were distinguished: atherosclerotic and aneurysmal. Representative examples of each are shown in Figs. 1 and 2. Forty-five limbs were atherosclerotic and 8 were aneurysmal in the series.

Patients had the usual ischemic symptoms characteristic of end stages of occlusive arterial disease with rest pain frequently associated with tissue loss predominating. A few had rapidly progressive intermittent claudication which had progressed to less than ½ block walking tolerance. If gangrene involved more than ½ of the foot, below knee amputations were performed without sympathectomy. All, including the few with

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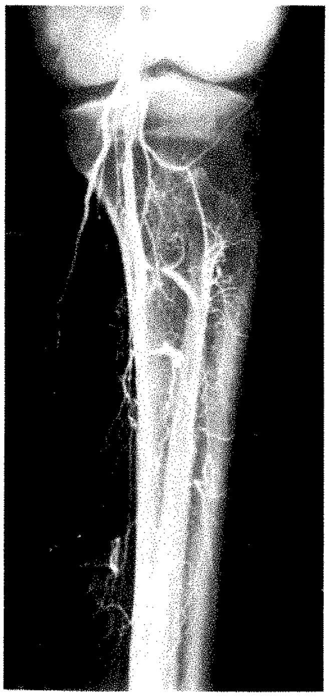

FIG. 1. Angiographic appearance of atherosclerotic occlusive disease. None of the distal tibial vessel is in continuity.

claudication, were thought to be candidates for early amputation.

A good result was manifested by one of the following: increased warmth of the skin associated with disappearance of rest pain, healing of tissue, however slow, and a generally nonpainful useful limb for at least 6 months after the operation. Improvement in exercise tolerance was also evaluated.

All patients who smoked were advised to stop and those with any walking tolerance were advised to walk one mile per day pushing themselves to the limits of pain tolerance. Antibiotics were liberally employed in the presence of open lesions.

A standard operative procedure was employed to achieve lumbar sympathectomy. The critical factor in the operative procedure was considered to be removal of the entire paravertebral lumbar sympathetic chain extending from the crus of the diaphragm to the crossing of the iliac vessels. The proximal transection was performed where the chain had a Y-configuration formed by the joining of the lowermost pre-ganglionic fiber to the ganglionated chain (Fig. 3) at the level of the crus of the diaphragm. A frozen section pathologic examination was routinely performed to confirm the presence of ganglion cells. The number of identifiable ganglia was quite variable.

Exposure for this extensive resection was achieved through a muscle splitting incision extending from the end of the 11th rib to the edge of the rectus sheath at the level of the umbilicus. The muscle layers were widely undermined along the direction of fibers. The kidney was mobilized anteriorly to permit access to the crus of the diaphragm.

Results

There were 4 deaths within one month of the operative procedure for a mortality rate of 6.5%. All deaths were from cardiac causes. There were 2 additional late deaths, one from a cerebral vascular accident, 6 months postop, and the other from carcinoma of the colon, one year postop. Of the 53 lumbar sympathectomies to be analyzed, 21 were performed for tissue loss, 19 for rest pain, and 5 for claudication of less than ⅓ of a block. The patients with claudication had rapidly worsened while under active treatment consisting of walking exercises. Although the series was almost equally divided between diabetic and non-diabetic patients, improvement was essentially the same for both groups, 62% for diabetics and 59% for non-diabetics (Table 1).

The improvement rate was greatest for those with claudication (100%). The improvement rate for those with tissue loss was 62% and for those with rest pain it was 47%. The severity of the occlusive process is illustrated

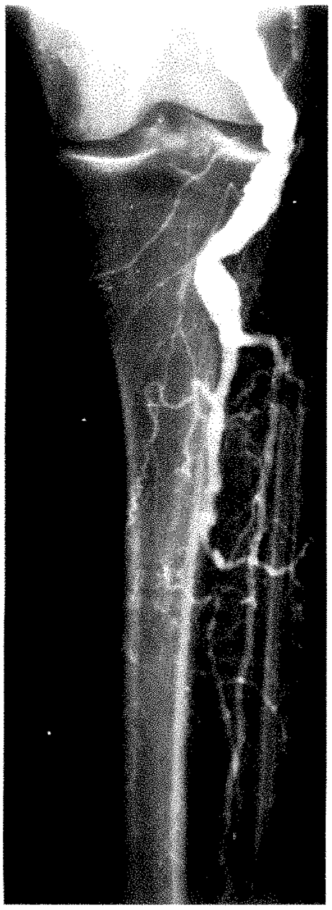

FIG. 2. Angiographic appearance of aneurysmal dilatation and distal occlusions.

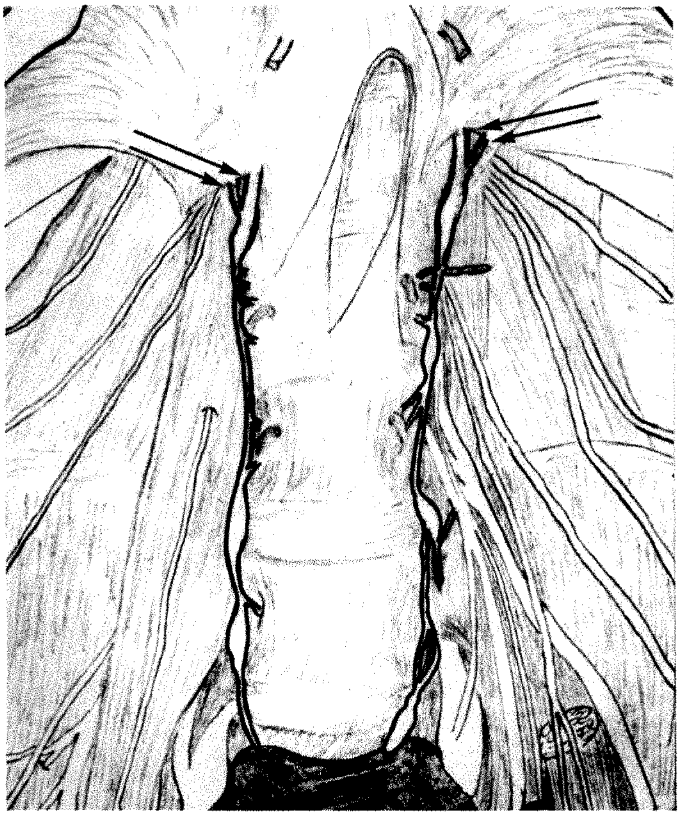

FIG. 3. Lumbar sympathetic chain; arrow showing uppermost lateral preganglionic fiber.

by the fact that those who did not show improvement underwent major amputations, for a rate of 38% for those with tissue loss and 53% for those with rest pain (Table 2). Amputations usually occurred within one to 2 months postop.

Patients with aneurysmal disease fared better. These were all considered to be inoperable on the basis of angiographic studies since all major tibial arteries were occluded. In this group there was one early amputation for a rate of 12% and one 2 years later for a total amputation rate of 25% (Table 3).

Discussion

The present series represents an easily defined group of patients with end stage arterial disease either due to atherosclerosis obliterans or thrombosed popliteal aneurysms with inoperable occlusion of tibial arteries. All patients were threatened with limb loss, and this is illustrated by the fact that those with tissue loss or with rest pain who did not improve following sympathectomy had an average early amputation rate of 40%. By inference then, 60% of this group might be considered to have avoided amputation due to a favorable response to sympathectomy. Indeed, many with intolerable pain expressed a desire to undergo amputation prior to improvement from sympathectomy.

TABLE 1. *Comparison of Results in Diabetic and Non-diabetic Patients*

	No. of limbs	Improved	Amp.
Diabetic	26	16	10
Non diabetic	27	16	11

TABLE 2. *Indication for Lumbar Sympathectomy and Results Tabulated by Degree of Limb Ischemia*

Symptom	# of limbs	Improved	Improvement Rate	Amp.	Amp. Rate
Claudication	5	5	100%	0	0
Tissue loss	29	18	62%	11	38%
Rest pain	19	9	47%	10	53%
Overall	53*	32	60%	21	40%

* Four patients with concomitent surgery and 4 postop deaths were excluded.

It is conceivable that the variability of the lumbar sympathetic chain may be a factor to be considered in the end results reported by various groups. Ordinarily, lumbar sympathectomy is reported as the removal of a given number of sympathetic ganglia, usually 3 or more. The lumbar sympathetic chain, however, varies widely in its morphology.[10]

Recognizable swellings of the chain, identifiable as ganglia, may vary from one to 4. By microscopy, synaptic junctures can be seen along the entire length of the chain. Indeed, even the pre-ganglionic inflow may vary in level from D12 to L1 or L2. A standardization of surgical technique therefore would be desirable to permit comparisons of results. the criteria that we have employed have been easily taught and are recommended as a basis for comparisons.

Varying physiologic effects of removal of sympathetic structures were recognized as early as 1855 by Budge.[3] A concern of many subsequent investigators, the phenomenon was the subject of the final monograph written by Dr. Walter B. Cannon.[4]

In essence, pre or post-ganglionic sympathetic interruption results in increased sensitivity of the end organs deprived of circulating adrenaline. The hypersensitivity produced by post ganglionic interruption is

TABLE 3. *Comparisons of Results in Atherosclerotic and Aneurysmal Occlusive Limb Ischemia*

		Amputations		
Disease	No. Limbs	Early	Late	Total
AS	45	17	2	19 (42%)
AN	8	1	1	2 (25%)

tenfold while that produced by preganglionic interruption is only threefold.

Although the reaction of blood vessels is generally conceded to be identical to that of smooth muscle and glandular structures, some differences of opinion exist.[6,7]

The supersensitivity of denervated blood vessels is not limited to reactions to adrenaline but includes reactions to histamine, acetylcholine, pituitrin, ergotoxine, cooling and excitement. Indeed, pain, vigorous muscular activity, exposure to cold and hypoglycemia, which are associated with increased discharge of adrenaline from the adrenal medulla, also elicit the exaggerated response on the part of denervated blood vessels. Telford[14] and Smithwick[11] attempted to apply these facts to the technique of upper dorsal sympathectomy, suggesting that only preganglionic interruption be performed.

The technique of denervation herein described achieves both decentralization (preganglionic) and denervation (postganglionic) interruption and from the physiologic data would seem to be less desirable than decentralization alone. Although this may be critical in the treatment of vasospastic disorders in which immediate beneficial effects of sympathectomy may be followed months later by relapses, it is not clear whether this plays a role in failures of sympathectomy for occlusive disease. Supersensitivity becomes manifest within 8 to 16 days after denervation while failures of sympathectomy are usually evident within hours postoperatively by failure of increased skin temperature to develop. In addition, immediate good results tend to persist.[13]

The pathologic process which results in the arterial occlusions appears to play a role in the results of sympathectomy. Ischemia due to occlusive aneurysmal disease responds more favorably to sympathectomy than that due to atherosclerotic occlusions. The precise reason is not clear although it is apparent that the widespread marked thickening of the walls of the arteries associated with atherosclerosis is not as evident in arteriosclerotic aneurysms.

The question of whether pathologic involvement of the sympathetic chain is part of the pathologic process of generalized arterial disease has also been suggested but never thoroughly explored as a possible cause of the unpredictability and variability of results. Pick, who performed extensive electromicroscopic studies of excised sympathetic chains suspected that the changes in mitochondria which he observed signified that autosympathectomy had occurred in many of these patients.[10] This has been debated at the clinical level.

The effect of lumbar sympathectomy has been and still is unpredictable. Many techniques have been used preoperatively to anticipate the clinical response, the latest being the so-called Ankle-Brachial systolic pressure index.[15] This is an attempt to measure collateral circulation of extremities. It is not possible for us to comment on this technique.

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Renovascular Hypertension From Renal Artery Compression by Congenital Bands

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Renal artery compression by fibromuscular bands containing sympathetic nerves and ganglia was encountered in 3 of 75 patients with renovascular hypertension. The hypertension was successfully managed by resection of the bands. The absence of mortality and morbidity dictates that the "stenotic" area of the renal artery be explored, especially in children and adults with minimal angiographic evidence of visceral atherosclerosis, before proceeding with a bypass graft to the renal artery.

APPROXIMATELY 2 to 10% of the 20 million hypertensive patients in the United States have renovascular hypertension.[8,18,21] Atherosclerosis is the underlying cause of the hypertension in 60 to 70% and fibrous and/or muscular dysplasia in 20 to 25% of the patients. Renal artery thrombosis, embolism, dissection, aneurysm, arteritis and venous fistula are responsible for approximately 5% of the cases. Regardless of the etiology, the hypertension caused by these lesions is usually treated by renovascular reconstructive procedures that are designed to improve blood flow through the stenotic area or to bypass the stenotic area.

Renovascular hypertension may also occur if renal arterial flow and pressure are reduced by external compression of the renal arteries by any of the retroperitoneal structures, e.g., ganglia,[24] adrenal glands,[28] tumors,[12,23,29] etc. A review of the literature has revealed 5 cases of renal artery compression by fibrous or muscular bands.[3,14,26] Recent experiences with three patients with renovascular hypertension resulting from compression of a renal artery by fibromuscular tissue containing neural components has prompted this report.

Case Report

The first patient was a 24-year-old Caucasian man with fatigue, weakness, and chest pain for five months, but with known hypertension for one month. Despite antihypertensive medication his symptoms increased and his blood pressure remained elevated.

Physical examination was normal save for a blood pressure of 150/100, a slightly enlarged heart, and a soft systolic pulmonic ejection murmur. His admission hemoglobin, white blood cell count, serum chemistries, electrocardiogram and chest films were normal. His creatinine clearance was 100 ml per minute. Urinary catecholamine concentrations were within normal limits. An aortogram (Fig. 1) revealed a normal artery to the right kidney. There were three arteries to the left kidney. There was delayed flow through the superior left renal artery which appeared to be partially obstructed 2 cm from its origin. There were 166 nanograms % of renin in the blood from the right renal vein and 266 nanograms % in the blood from the left renal vein. The inferior vena cava blood contained 200 nanograms % of renin.

At operation on November 19, 1973, a band of tissue, approximately 2 cm lateral to the aorta, which pulled the left superior renal artery posteriorly was found to be responsible for the "kink" and obstruction in the artery. The band appeared to be composed of the aortico-renal ganglia anteriorly and was attached to fibromuscular slips of the diaphragm posteriorly. After portions of the ganglion and fibromuscular band were removed, the artery assumed a normal contour and appeared to have normal blood flow. After the obstruction was relieved no gradient could be demonstrated across the area of the previous constriction. The patient tolerated the operation well. Postoperatively his blood pressure returned to normal and during followup visits it has remained in the 140–150/80–90 range.

The material removed contained portions of sympathetic ganglion and fibromuscular tissue (Fig. 2).

The second patient was a 4¾ year-old Caucasian boy with known hypertension for two months. His previous medical history and his family history were noncontributory. He had been evaluated at his local hospital one month prior to his admission to the Duke University Medical Center and had had a normal intravenous pyelogram. His serum chemistries and urinary catecholamine concentrations were also normal.

On admission he had a blood pressure of 135/100. The remainder of his physical examination was normal. His serum chemistries, urinalysis, hemoglobin, white cell count, electrocardiogram and chest x-rays were normal.

A repeat intravenous pyelogram was normal. Urine catecholamines

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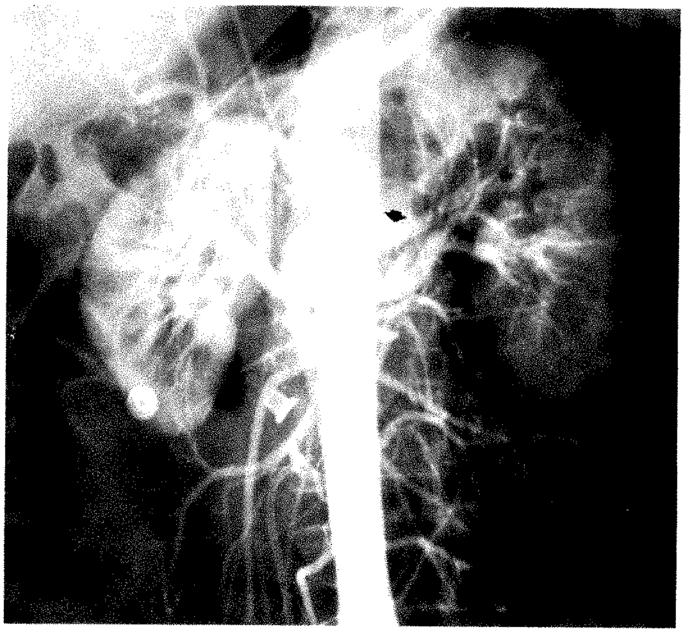

FIG. 1. The single right renal artery is normal. The superior left renal artery is severely kinked (arrow) and partially obstructed about 2 cm from its origin.

were normal. Peripheral blood samples contained 428 nanograms % of renin. An aortogram (Fig. 3) revealed a severe stenosis about 2 cm to the left of the origin of the left renal artery. A post stenotic dilatation was present. The three renal arteries on the right appeared normal. Blood samples were collected from the renal veins and contained 333 nanograms % of renin on the left, and 260 on the right. The inferior vena cava blood contained 300 nanograms % of renin.

On May 30, 1974, a fibrous band was found to be constricting the left renal artery. The band was divided and a portion removed. After this was completed the renal artery appeared normal and the previous thrill could not be detected. In order to be sure that there was not an intimal or medial lesion, the artery was opened longitudinally. The internal aspects of the artery were normal and the artery was closed with a vein patch. The patient tolerated the operation quite well. His postoperative blood pressure was 120/70. Microscopic study of the specimen revealed fibrous tissue containing ganglion cells (Fig. 4).

The third patient was a 33-year-old Caucasian woman who had a 10-year history of hypertension which had become progressively more severe and unresponsive to treatment. Physical examination revealed a blood pressure of 188/130, a moderately enlarged heart and narrowing of the retinal arteries.

Her serum chemistries were normal except for a mild increase in triglycerides. Her electrocardiogram demonstrated left ventricular hypertrophy. Urinary VMA's were normal. Creatinine clearances were 77 and 86 ml per minute. Plasmin renin assays revealed: a peripheral renin of 328 nanograms %; vena cava, 400 nanograms %; left renal vein, 428 nanograms %; and right renal vein, 628 nanograms %. An aortogram revealed a moderate degree of stenosis of the origin of the right renal artery and post stenotic dilatation (Fig. 5). The left renal artery appeared normal.

On November 29, 1974, the right renal artery was explored. About 1 cm beyond its origin the right renal artery was compressed by a band which appeared to be a part of the aorticorenal ganglion. A portion of the band was excised and the artery mobilized. Following

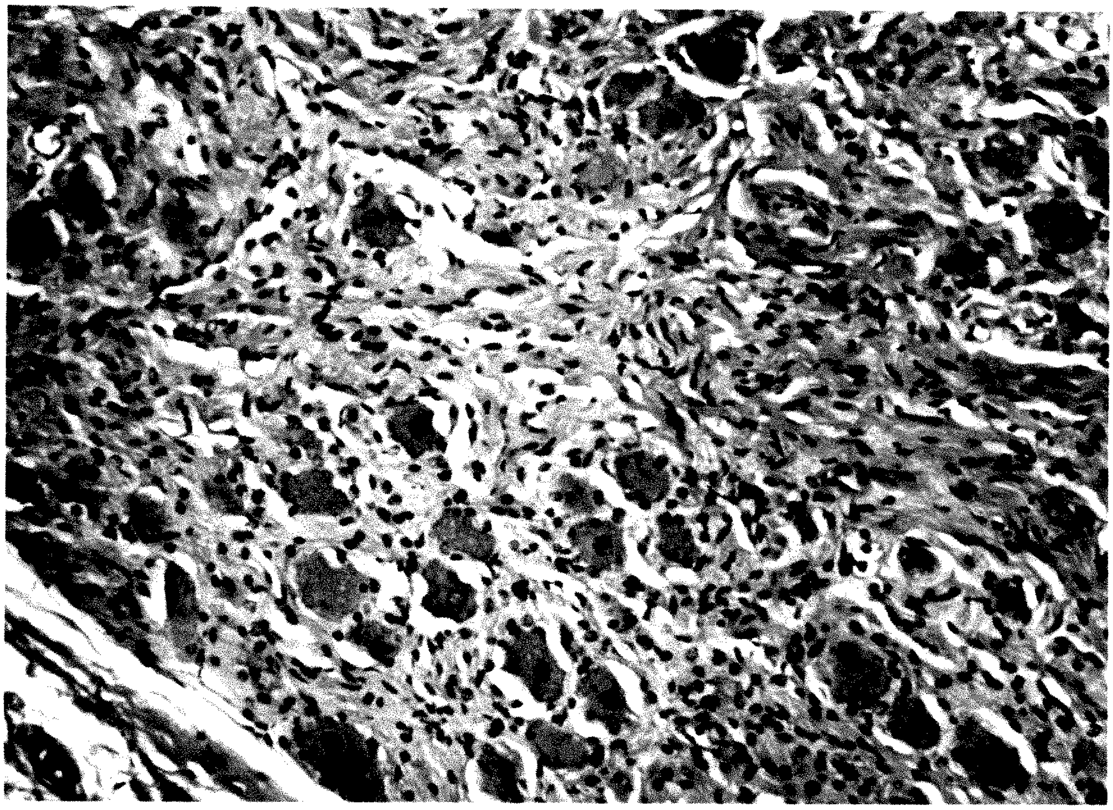

FIG. 2. Microscopic study of the band revealed fibromuscular tissue containing sympathetic ganglia.

this the thrill could not be palpated, the artery was not distorted, and a pressure gradient could not be demonstrated across the area.

She tolerated the operation well, and has done well postoperatively with blood pressures in the 135–150/90–100 range. Her current medications include Diazide, 1 capsule twice a day, and Inderal, 40 mg four times a day.

Microscopic study of the specimen showed fibromuscular tissue containing a few small vessels and nerve bundles (Fig. 6).

Discussion

Although Richard Bright suggested a causal relation between renal disease and hypertension[1] it wasn't until 1934 that Goldblatt clearly demonstrated a renal etiology for hypertension.[9] In 1937, Butler successfully initiated the surgical management of renal hypertension by removing a pyelonephritic kidney in a 7-year-old child.[2] Thompson and Smithwick, in 1952, unsuccessfully attempted to treat hypertension by renal revascularization.[27] One of the earliest successful renal artery reconstructions occurred in 1956 when Poutasse inserted bilateral bypass grafts (femoral artery homografts) in a 14 year old with renovascular hypertension.[22] Since 1956 renovascular hypertension has been recognized with increasing frequency and now is responsible for about 5% of the cases of hypertension.

Atherosclerosis is responsible for renal artery obstruction in 60–70% of the cases of renovascular hyper-

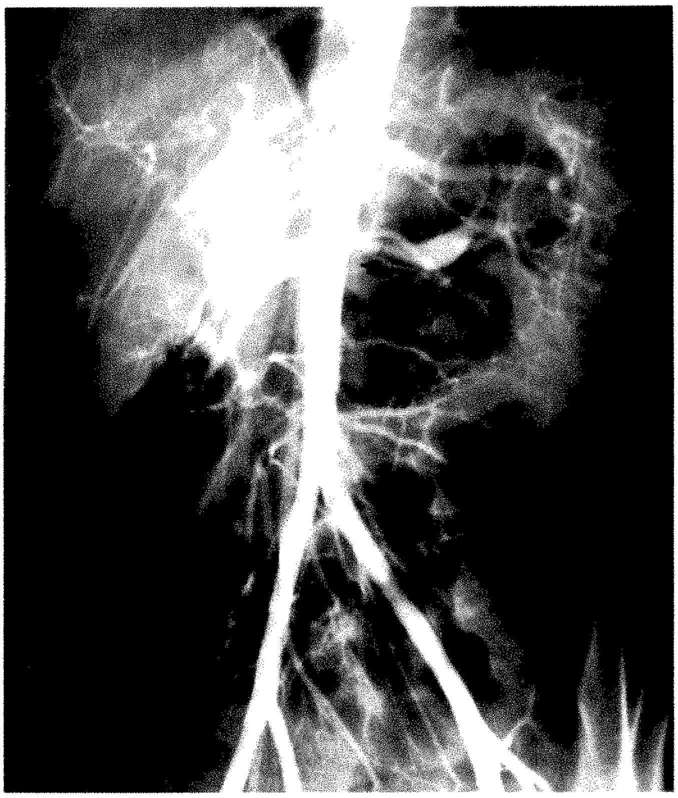

FIG. 3. A very tight stenotic area with a post-stenotic dilatation was demonstrated in the left renal artery.

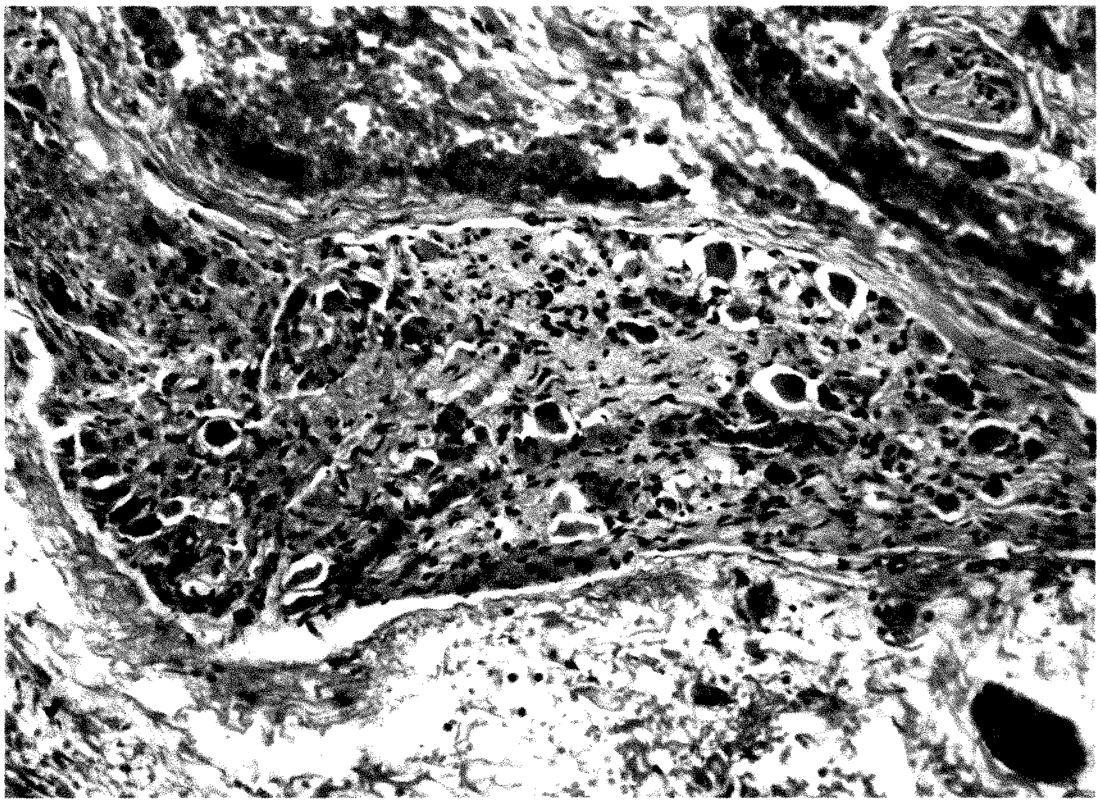

FIG. 4. The fibrous band contained nerve fibers and ganglia.

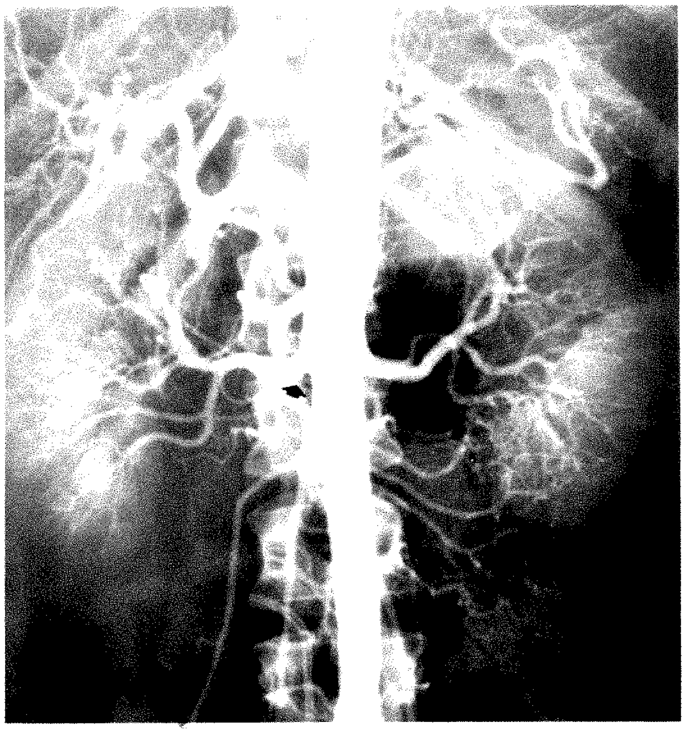

FIG. 5. The aortogram demonstrated a tight stenosis at the origin of the right renal artery with a post-stenotic dilatation.

tension.[5,16,19,25] Most often the atherosclerotic stenosis occurs at the origin of the renal artery and is associated with changes in the aorta and other visceral vessels. This form of renal artery obstruction is most often treated with a bypass graft with an endarterectomy being the second most commonly performed procedure.

The second most common cause of renal artery obstruction is the intimal, fibrous, and muscular dysplasia that occurs in the renal arteries.[7,11,26] The type of reconstructive operation for this type of obstruction is dictated by the disease process; it may entail bypass graft, patch graft, dilatation, etc.

The operative mortality for these operative procedures vaires from 0[4] to 15%[30] with the average mortality rate being 4%.[15] Approximately 6 to 13% of the patients operated upon require secondary nephrectomies.[6,13]

Less than 5% of the renal artery occlusions or compressions are caused by tumor, arteritis, aneurysm, fistula, etc. An even smaller number of cases of renovascular hypertension is caused by extrinsic compression of a renal artery by a fibromuscular band which may contain neural tissue. Sympathetic nerves and ganglia were described in two of the 5 fibrous compressive bands found during a literature review.[26] Nerve fibers and/or ganglia were demonstrated in the fibrous bands of the three patients described in this report. The fibrous bands have been described as arising from the psoas minor tendon or diaphragm.[3] The fibromuscular band in one of our patients appeared to be associated with the diaphragm. The bands in the other two cases appeared to be a portion of the aorticorenal plexus and not the diaphragm or other retroperitoneal fibrous structures.

Although the precise embryologic occurrence respons-

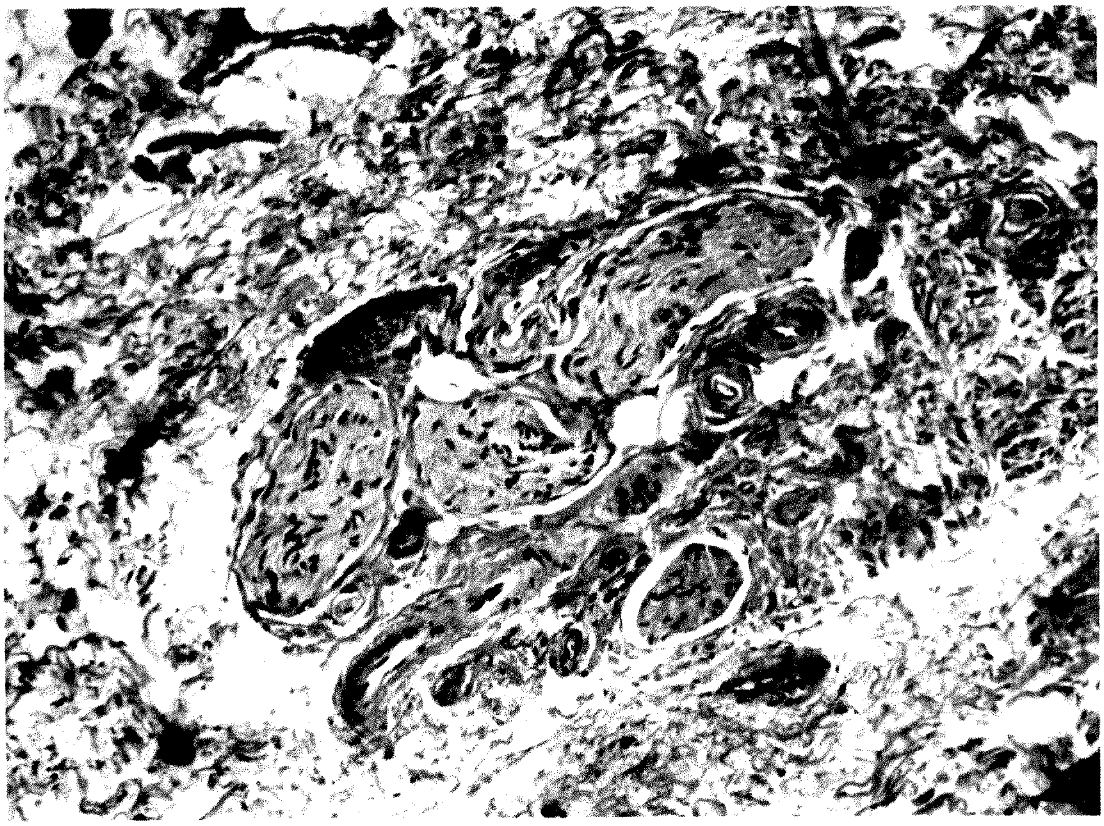

FIG. 6. The fibromuscular band contained bundles of nerves.

ible for the congenital compressive bands cannot be defined, it would appear that abnormalities of the cephalad migration of the kidneys, its blood supply and/or abnormalities of the development of the aorticorenal sympathetic plexus could be responsible. The kidneys begin relatively low in the embryo and by caudad growth of the body and cephalad growth of the kidney, the kidneys ascend in the retroperitoneal space. "During ascent of the kidneys their intrinsic blood vessels receive their blood supply from lateral stem arteries which arise from the aorta at increasingly higher levels until that of the definitive renal arteries, at the second lumbar vertebra, is reached."[10]

The nerves to the kidney arise from the aorticorenal ganglia, the middle and inferior splanchnic nerves and the lumbar sympathetic chain and accompany the renal vessels. The nerves lie on the renal arteries and are joined together by transverse oblique and circular fibers which encircle the renal arteries.[17] It is not unreasonable to speculate that a fibrous or muscular band from the diaphragm or psoas minor muscle could block the cephalad "migration" of the arterial supply so that a kink would occur. One might even speculate why this doesn't occur more often. It is also not inconceivable that the circular neurofibers could persist and constrict a renal artery as it enlarges to adult size.

The true incidence of extrinsic renal artery compression by congenital bands is unknown because the arteriographic appearance of the lesion may mimic that of atherosclerotic occlusive disease and because frequently renal artery lesions are bypassed with an aorticorenal or iliorenal bypass graft and the "stenotic" areas are not visualized. The angiographic demonstration of a stenotic area in a renal artery of a child or in an adult without significant atherosclerotic disease in the aorta or the other visceral arteries should raise the possibility of a compressive band around the renal artery. The finding of only 5 cases in the literature would suggest that the incidence is very low, however the finding of 3 cases among 75 patients operated upon at the Duke University Medical Center[20] for renovascular hypertension suggests that the incidence is probably significant and may be related to the frequency with which the "stenotic" lesion is explored.

There was no operative mortality in the 3 cases in this report or in the 5 cases in the literature. The morbidity has been negligible because renal arterial reconstruction has not been necessary in any of our cases. One case in the literature had a dacron bypass graft[14] in addition to the removal of the stenosing band. The renal artery of one of our cases was opened to be certain that an intimal or medial hypertrophy was not present. Four of the 5 patients in the literature had return of their blood pressure to normal as did 2 of the 3 patients included in this report. The blood pressure of our third patient returned to the pre-existing "essential hypertension" levels after division and partial removal of the band constricting her renal artery.

The ease with which a stenosing band around a renal artery can be removed and the salutory effect of the removal upon the renovascular hypertension dictate that the "stenotic" area of a renal artery be explored in all children with renovascular hypertension and in all adults with minimal evidence of atherosclerotic vascular disease before the stenotic area is bypassed. It is anticipated that more bands which constrict the renal arteries will be encountered as more of the arteries are adequately explored.

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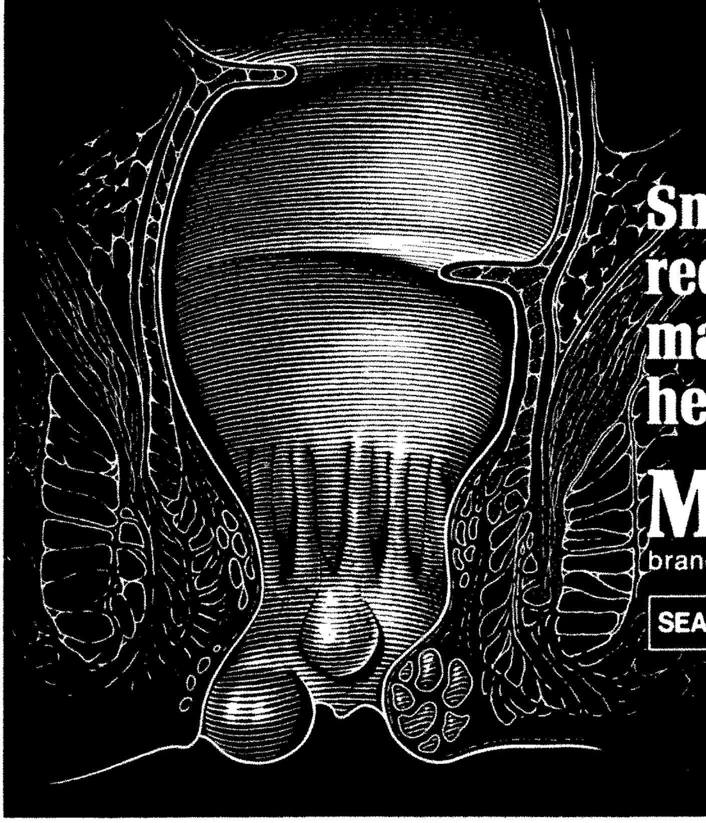

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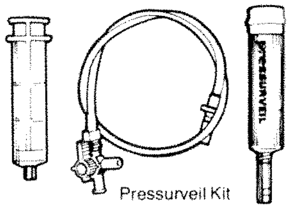

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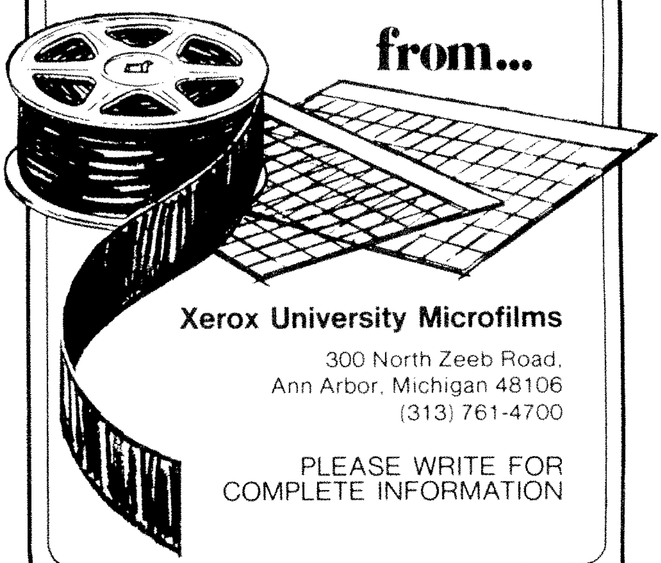

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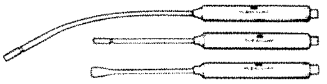

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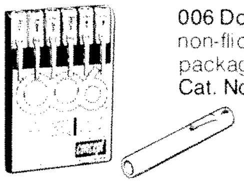

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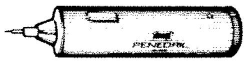

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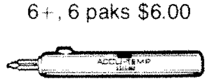

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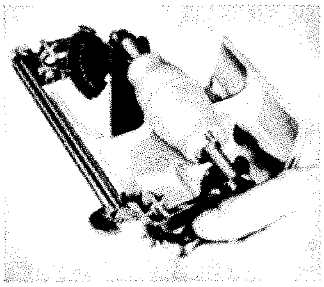

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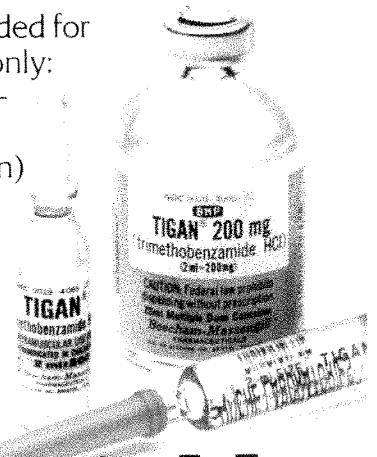

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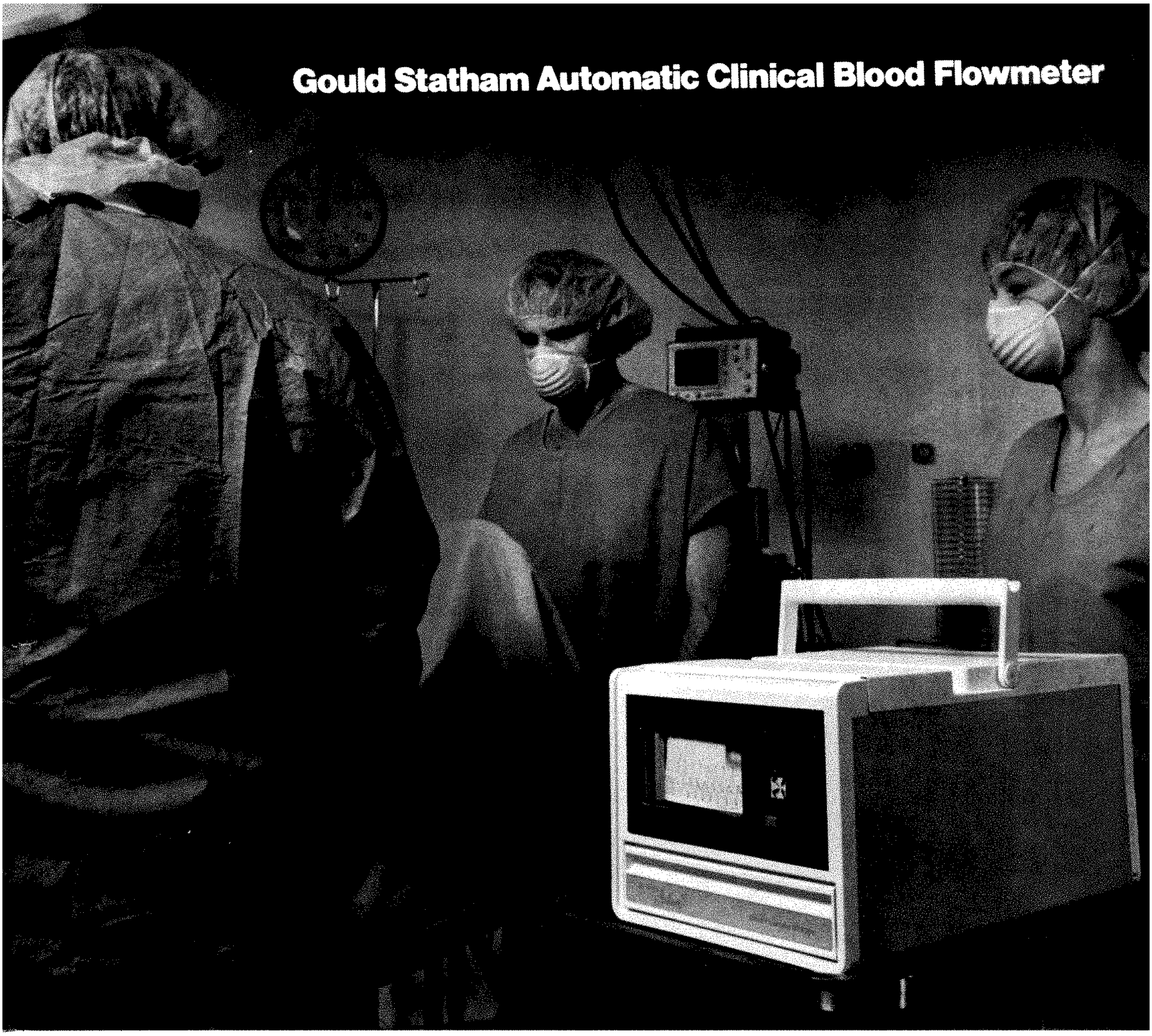

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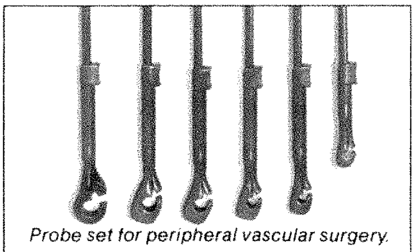
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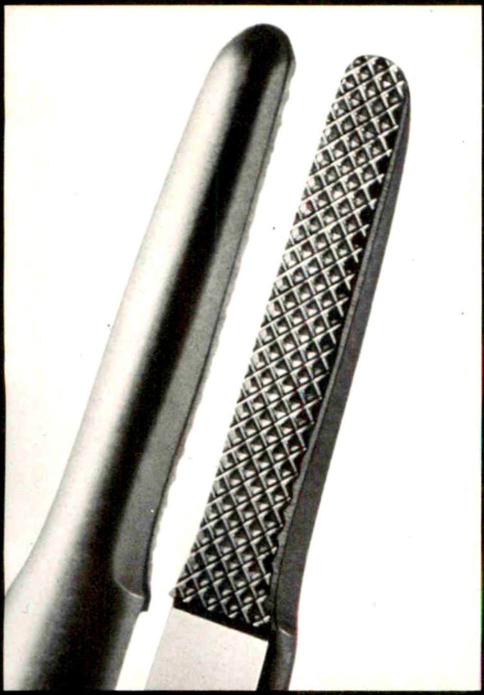

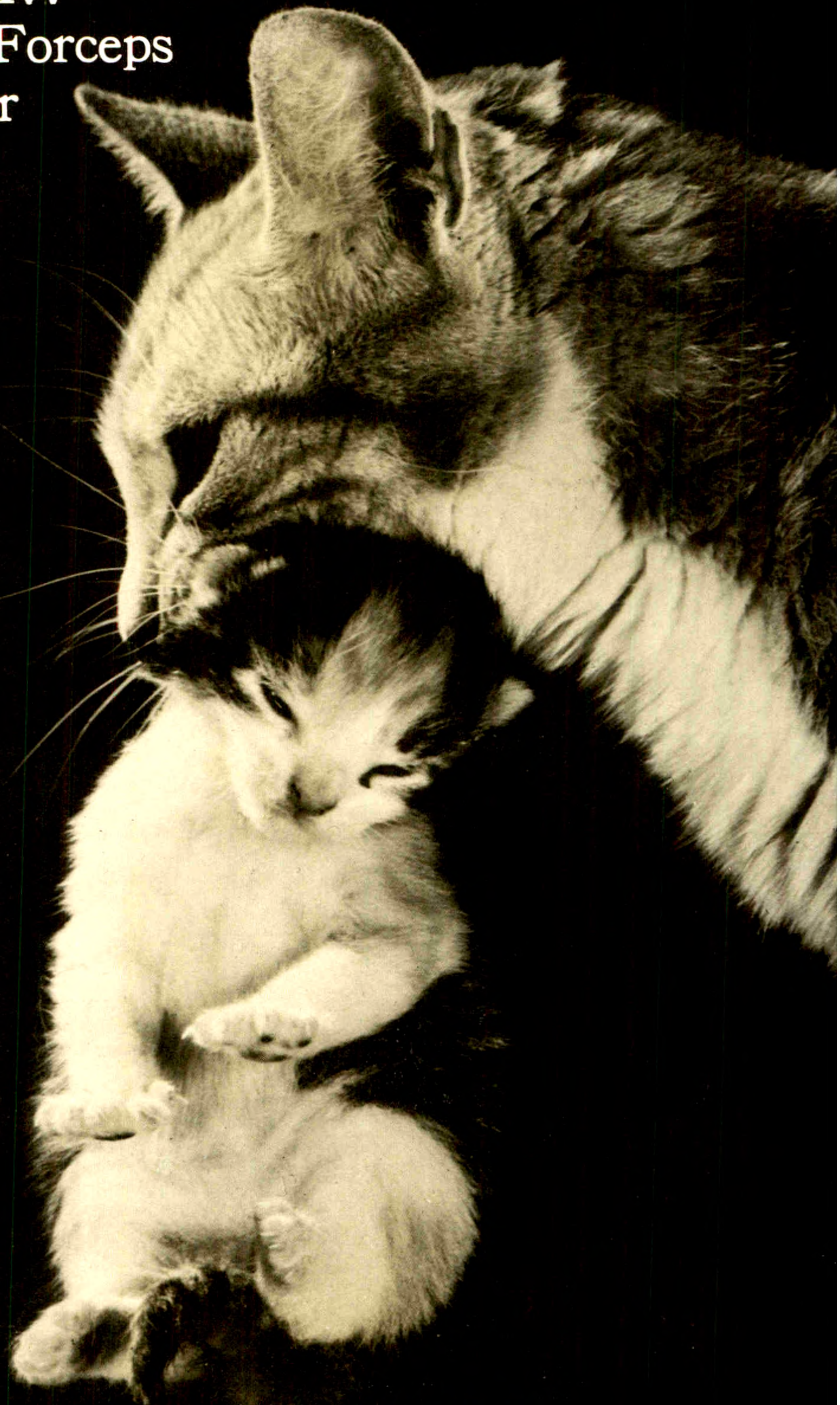

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Basal and Meat Extract Plasma Gastrin Before and After Parietal Cell Vagotomy and Selective Gastric Vagotomy with Drainage in Patients with Duodenal Ulcer

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Basal and meat extract stimulated plasma gastrin (PG) levels and basal and stimulated gastric acid secretion were evaluated pre and postoperatively in duodenal ulcer patients who underwent parietal cell vagotomy without antral drainage (normal duodena) (PC, n = 32) or selective vagotomy with drainage (pyloric stenosis) (SV + P, n = 11). Before operation, both groups had comparable basal PG values of 52 ± 13 pg/ml (PCV) and 51 ± 18 pg/ml (SV + P), while the peak gastrin level to meat extract stimulation was 173 ± 40 pg/ml for the total group of patients. After both operations basal PG levels increased (107 ± 18 pg/ml (PCV) and 152 ± 45 pg/ml (SV + P)) and the gastrin response to meat extract stimulation was augmented after PCV, while the response after SV + P was the same as before operation. Patients with PCV often demonstrated an acid response following meat extract stimulation (3.6 ± 0.9 mEq HCl/hr), and pentapeptide stimulation (18.8 ± 2.0 mEq/hr) while patients with SV + P showed a minimal response (1.3 ± 1.2 mEq HCl/hr meat extract), and 10.7 ± 1.8 mEq/hr pentapeptide stimulation. The comparatively intact acid responses in the PCV patients may augur a high ultimate recurrence rate.

IN THE PAST DECADE, operations for duodenal ulcer have become more conservative of gastric mass with a tendency to interfere less with physiologic function. Associated with this has been an apparent increase in recurrence of duodenal ulcer,[11,12,34] especially following vagotomy and drainage as compared with hemigastrectomy or antrectomy with vagotomy.[12,26] The newest of these gastric-mass-conserving operations, parietal cell vagotomy without drainage in patients without pyloric stenosis has enjoyed popularity in England and Europe.[1,3,25] It appears to give early clinical results which are quite satisfactory and without interference in gastric emptying.[1,7,21]

The physiological principle of this operation is that while the parietal cell mass of the stomach is denervated, the antrum is left innervated and drainage is not required. While insulin-stimulated acid secretion often disappears and stomach emptying is normal after PCV in dogs,[1] this operation results in an enhanced acid response to feeding and an aproximately 50% increase of the 24 hour Heidenhahn Pouch acid secretion,[1,2] suggesting increased secretion of antral gastrin.

In the following study, basal and meat extract stimulated plasma gastrin (PG) levels pre and postoperatively and acid secretion in response to insulin hypoglycemia, pentagastrin, and meat extract stimulation were evaluated in duodenal ulcer patients before and after parietal cell vagotomy (PCV), and in those patients with pyloric stenosis, selective vagotomy and pyloroplasty (SV + P). Postoperatively, patients were divided into insulin negative and insulin positive groups, and the co-variation of the meat extract stimulated acid secretion and plasma gastrin levels determined. The results indicate that considerable acid secretion responsiveness remains after parietal cell vagotomy, and that this may be correlated with the elevated levels of gastrin seen in response to meat extract stimulation.

Material and Methods

Forty-three patients were studied at the Kommune Hospital in Copenhagen, Denmark, 5 women and 39 men, with a mean age of 57 years (range 22–76 years). At operation, a duodenal ulcer was found in 42 patients and no ulcer in 1 patient. In 32 patients in whom no pyloric

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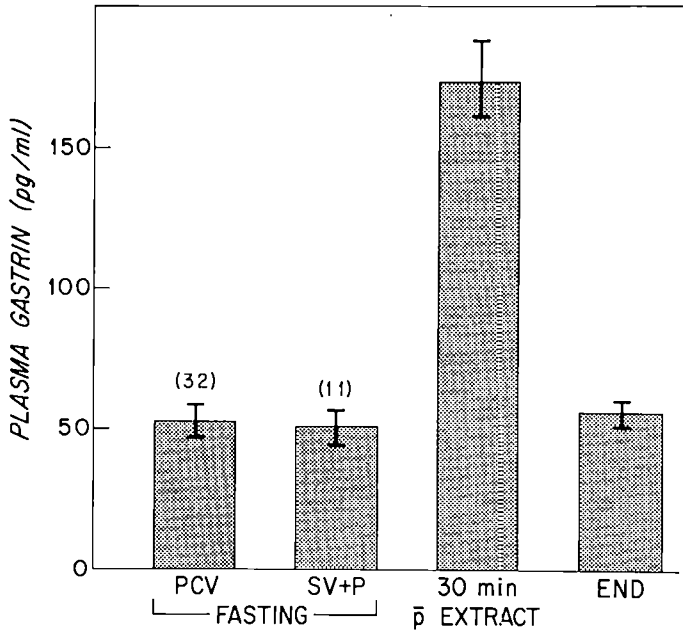

FIG. 1. Mean basal plasma gastrin levels ± SEM in both groups of patients and mean meat extract stimulated plasma gastrin ±SEM of the total number of patients before operation. Number of patients in each group are given in parenthesis.

stenosis was found, PCV was performed while in 11 patients with varying degrees of pyloric stenosis, SV + P was performed.

Samples for fasting PG were drawn on two separate occasions in 43 patients before operation and in 36 patients between 2 and 3 months after operation. Meat extract stimulation, which was done in 25 patients before operation and in 21 patients after operation, was only slightly modified.[10] PG samples were obtained 30 minutes after the meat extract stimulation, and at the end of the stimulation. The gastrin levels were measured by a sensitive radioimmunoassay method.[9] The samples were coded by number and the code broken only after the results were recorded. Each sample was assayed at least twice.

Gastrin Radioimmunoassay

Preparation of antigen was similar to that described by McGuigan.[35] Five mg of synthetic human gastrin, residues 2–17 (2–17 SHG, Imperial Chemical Industries) were added to approximately 2.2 × 10^6 cpm of labelled ^{125}I 2–17 SHG, and mixed with 10 mg bovine serum albumin in 0.33 ml 0.05 M pH 7.4 potassium phosphate buffer. Carbodiimide, (1-ethyl-3) (-3-dimethyl-amino-propyl) 42 mg was added and the reaction allowed to proceed for 20 hr at 20 C. After dialysis for 24 hr, approximately 9.3 moles of 2–17 SHG were coupled per mole of bovine serum albumin. The conjugated material was mixed with Freund's adjuvant and injected into the toepads of four rabbits. Rabbits received booster shots 6 months later and were bled 7 days later via the central ear artery. Serum obtained from one of the four rabbits was used as antibody in a final dilution of 1:150,000.

For the radioiodination of gastrin 1 ug SHG 1–17 was added with 100 μl pH 7 0.5 M phosphate buffer to 2 mCi carrier-free ^{125}I in 8 μl NaOH. Chloramine-T was used as an oxidizing agent. The reaction was allowed to proceed for 60 seconds according to the method of Hunter and Greenwood.[20] Sodium bisulphite (2.5 mg/ml) in pH 7.4 0.5 M phosphate buffer was used to stop the reaction. The resultant product was then applied at 4 C to a G10 Sephadex column of 12 ml capacity with a drip rate of approximately 1 per 20 seconds. The labelled peptide appeared in the void volume. Estimated specific activity was generally 250 mCi/mg. The labelled peptide was then further purified by starch gel electrophoresis.

Assay Technique

Incubation components of the radioimmunoassay for gastrin were 50 μl of the plasma sample to be assayed, 250 μl 0.02 M Barbital buffer (pH 8.2), 2,000 cpm ^{125}I 1–17:SHG in 100 μl Barbital buffer and 100 μl 1:30,000

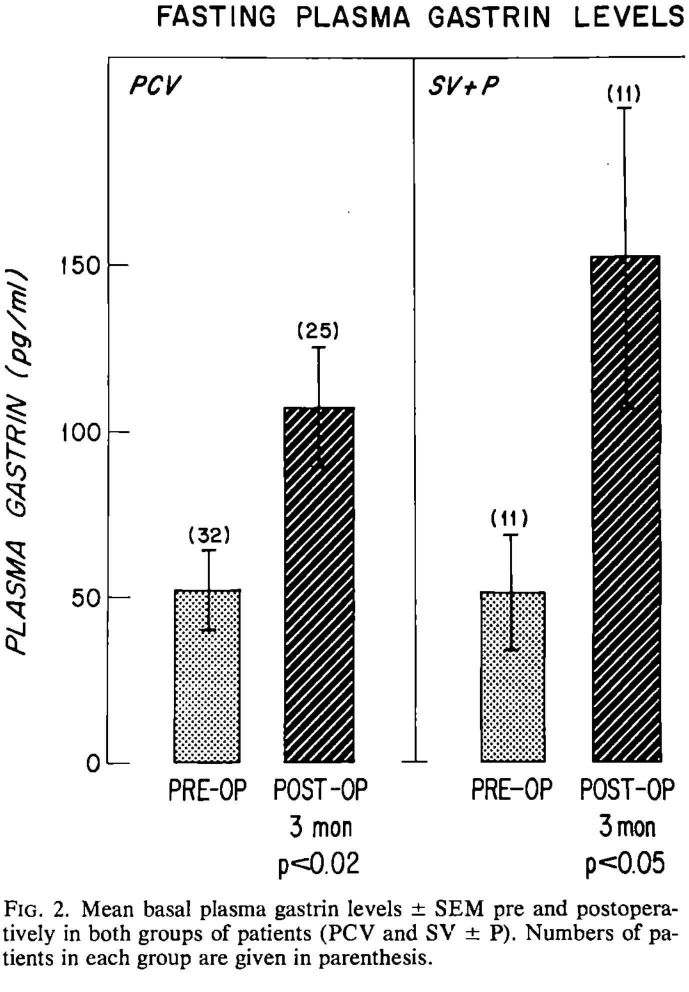

FIG. 2. Mean basal plasma gastrin levels ± SEM pre and postoperatively in both groups of patients (PCV and SV ± P). Numbers of patients in each group are given in parenthesis.

rabbit antigastrin antibody, making a final antibody dilution of 1:150,000. The mixture was incubated for up to 4 days at 4 C. Separation was achieved with 200 μl dextran-coated charcoal, supernatant decanted after centrifugation, and both bound and free components counted. Determinations were carried out in triplicate, with triplicate "damage" tubes to which no antibody had been added. Standard curves were obtained by adding known quantities of SHG 1:17 to human plasma which had been rendered gastrin-free by washing with dextran-coated charcoal. The coefficient of variation for the assay using this technique was 5 ± 1.3%. By this technique, gastrin can be accurately assayed from 16–1,000 pg/ml and levels above 1,000 pg/ml can be measured by dilution of the plasma sample with degastrinized plasma. The normal values for plasma gastrin (PG) levels were 0–150 pg/ml; approximately 35% of patients without demonstrable gastrointestinal disease have undetectable values (less than 16 pg/ml).

Gastric Acid Secretion

Gastric acid secretion studies were carried out preoperatively and between two and three months postoperatively.

The pentapeptide test was performed by stimulation with 6 microgram Peptavlon (ICI)/kg sc before the operation (25 patients) and with 10 microgram Peptavlon/g sc after the operation (19 patients). These doses have previously been shown to elicit maximal acid output both before and after PCV.[25] The insulin test was performed by stimulation with 0.2 IU/kg iv in 12 patients before and in 22 patients after operation.

The meat extract test was done in 25 patients before and in 21 patients after operation, only slightly modified after Giles and Clark (1966). Three oxo cubes were dissolved in 200 ml warm water and pH adjusted to 7.0 by adding 15–20 ml of 8% sodium bicarbonate. This solution was introduced into the stomach via nasogastric tube and left in the stomach 15 minutes with the patient in a sitting position. The stomach was then emptied by 5 minute aspirations with the patient supine. The stomach was rinsed with 200 ml of water and emptied by a further 5 minute aspiration. The entire procedure lasted about 30 minutes.

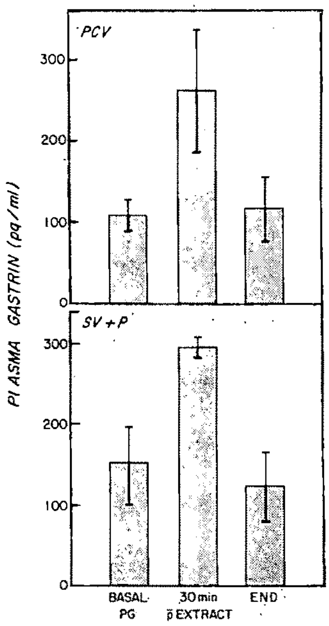

FIG. 3. Mean basal and meat extract stimulated plasma gastrin levels ± SEM postoperatively in both groups of patients (PCV and SV + P).

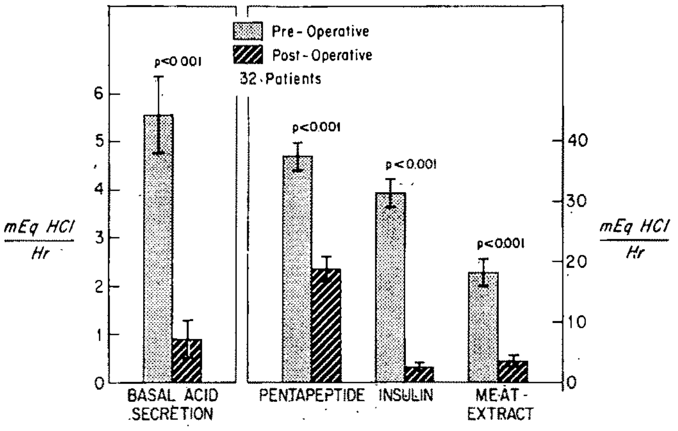

FIG. 4. Mean basal stimulated gastric acid secretion in response to pentagastrin, insulin hypoglycemia and meat extract pre and postoperatively in the parietal cell vagotomy group. Although there were 32 patients in the entire group, not all patients underwent testing pre and postoperatively. The numbers of patients in whom each test was carried out are given in the text.

All tests were done after an overnight fast. Gastric tubes were placed under fluoroscopic control with the patients supine. Aspiration was performed by intermittent pump suction, which was constantly supervised; aspirates were collected every 15 minutes.

For meat extract stimulation, the first 15 minute aspirate obtained before stimulation was designated "fasting secretion" and the next four 15 minute aspirates designated "basal secretion."

After pentapeptide or meat extract stimulation, six 15 minute aspirates were collected. After insulin, there were nine 15 minute aspirate collections. For each 15 minute aspirate, volume, pH (Radiometer) and acidity (by Titration to pH 7.0) were measured. Maximal acid production is expressed as "peak acid output" (PAO), the highest acid production in two consecutive 15 minute periods multiplied by two (mEq/hr). There was undoubtedly some loss of acid secretion, especially after SV + P, but no attempt was made to correct for this.

Statistical treatment of the results involved the calculation of mean values and standard errors of the mean and statistical analysis of differences in group means, was by use of unpaired Student's t-test. In the text, data are

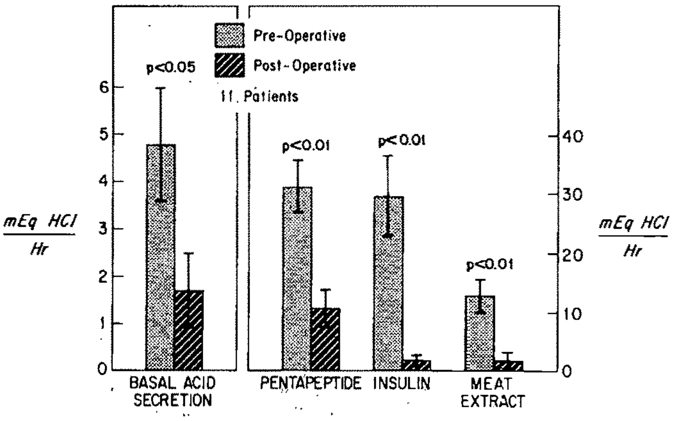

FIG. 5. Mean basal and stimulated gastric acid secretion in response to pentagastrin, insulin hypoglycemia and meat extract pre and postoperatively in the group who underwent selective vagotomy and pyloroplasty. Eleven patients are included in the total group. All underwent all tests before and after operation.

given as a mean ± SEM and wherever the word "significant" is used, it indicates a calculated P value of less than 0.05.

Results

Preoperatively, both groups had comparable mean basal PG values of 52 ± 13 pg/ml (n = 32) in the group that underwent PCV, and 51 ± 18 pg/ml (n = 11) in the patients in whom SV + P was performed. After stimulation with meat extract, the mean PG value of the total group of patients had risen 30 minutes after stimulation to 173 ± 40 pg/ml (Fig. 1). By 90 minutes, this had fallen to a mean of 56 ± 10 pg/ml, almost exactly the basal level.

Postoperatively, the mean basal PG increased significantly in both groups to 107 ± 18 pg/ml ($P < 0.02$) in the PCV group and to 152 ± 45 pg/ml ($P < 0.05$) in the SV + P groups (Fig. 2). There was a considerable gastrin response to the meat extract stimulation after both operations. The mean basal PG rose to 260 ± 74 pg/ml, 30 minutes after stimulation in the PCV group, while after SV + P the PG rose to 300 ± 13 pg/ml (Fig. 3). After 90 minutes, PG levels returned to 117 ± 38 pg/ml (PCV) and 126 ± 44 pg/ml (SV + P). When the gastrin response to meat extract stimulation is defined as the peak PG level after stimulation minus the basal PG level, the mean gastrin response after PCV was 160 pg/ml, in comparison to preoperative values 118 pg/ml, but the difference was not significant ($P = 0.60$). Gastrin response to meat extract stimulation after PCV was not significantly different from after SV + P ($P = 0.50$).

Following operation, acid secretion response to all stimuli was decreased. Basal acid secretion (BAO) in the PCV group was only 0.9 ± .04 mEq/hr and rose to 3.6 ± 0.9 mEq/hr after meat extract stimulation, and to 18.8 ± 2.0 mEq/hr after pentapeptide stimulation. Insulin stimulated secretion fell to 2.5 ± 0.7 mEq/hr (92% reduction), the greatest reduction of all groups (Fig. 4). In the SV + P group, BAO was 1.7 ± 0.8 mEq/hr. Following insulin stimulation, only 1.1 ± 0.6 mEq/hr was secreted and following meat extract stimulation, 1.3 ± 1.2 mEq/hr (Fig. 5). When patients were grouped postoperatively according to their insulin test, there was no significant difference in basal and meat extract stimulated PG levels between insulin negative and insulin positive patients in both groups (Table 1). After PCV, however, there was a positive relationship (correlation coefficient = 0.62) between meat extract stimulated PG levels and gastric acid response (Fig. 6) with a slope significantly different from zero at the $P = 0.05$ level.

Discussion

In spite of the demonstrated low recurrence rate following hemigastrectomy and vagotomy,[12,17,26] the occasional poor result following major gastric resection, especially in the underweight female, has led many investigators to seek operations for peptic ulcer which, while reducing the acid producing capacity of the stomach are conservative of gastric mass. The newest of these operations is the parietal cell vagotomy, in which the parietal cell mass is denervated while the motor innervation of the antrum, which aids gastric emptying, is

TABLE 1. *PG Levels and Gastric Acid Secretion 2–3 Months after PCV And SV + P*

Patient No.	Basal PG (pg/ml)	PG 1 Hr. After Meat Extract Stimulation (pg/ml)	Basal Acid Secretion (mEq/hr)	Acid Secretion 1 Hr. After Meat Extract (mEq/hr)
After PCV				
7.615 − I	85	240	0	0
24.809	60	165	0	3.7
25.326	125	450	0	8.1
25.728	20	170	0	3.2
25.746	25	300	0	4.8
25.868	38	210	0	9.8
25.947	20	100	0	0.1
26.076	20	130	0	0
26.422	100	200	0.4	6.1
26.498	200	250	0	0
After PCV				
25.730 + I	49	50	0.2	1.5
26.158	70	140	0.2	1.1
26.160	70	215	0	1.9
26.402	350	1240	4.5	9.8
After SV + P				
24.776 − I	100	—	0	0
25.646	120	20	0.7	0
26.012	20	150	0.2	0
After SV + P				
25.643 + I	145	210	0	0
25.682	510	800	2.0	0.4
26.543	130	320	7.5	7.7

Note: −I = insulin negative; +I = insulin positive.

left intact, as is the neural arc in the release of antral gastrin. Acid inhibition from the parietal cell mass, the most potent feedback mechanism inhibiting the release of antral gastrin, is diminished. This would seem, superficially at least, a possible ulcerogenic situation, but the early reports, notably from centers in England and Scandinavia have been enthusiastic.[4,8,19,23,25,32,41] While sufficient time has not elapsed for late recurrences, the early recurrence rate is still very low and well below the 2% level,[13,16,18,25] except for one recent report.[27]

The results reported herein confirm that in a group of ulcer patients whose preoperative fasting PG does not differ significantly from basal levels in other patients with duodenal ulcer,[36,39,40] fasting plasma gastrin increases significantly following parietal cell vagotomy.[22,31,33,38] The data are still only at variance with those reported by Clark, *et al.*[6] The gastrin response to meat extract stimulation was increased after PCV and remained unchanged after SV + P. This is in accordance with the findings of Jaffe, et al.[22] and again at variance with the findings of Clark and co-workers,[6] who found a decrease in gastrin response to oxo-meat extract stimulation after PCV. These results need not be surprising, as it has been amply demonstrated that different laboratories using different antibodies, or indeed the same laboratory using different antibodies[15] may be measuring different components of circulating gastrin, and that these components presumably change with stimulation.

After truncal, selective and parietal cell vagotomy, basal plasma gastrin levels are increased significantly, perhaps because of the reduction of acid inhibition[14,30] and after truncal vagotomy, probably also due to section of extra gastric vagal fibers.[28,31] Although gastrin released from duodenal and other sources may be increased following vagotomy, this form of gastrin may perhaps be less potent in evoking acid production. Since column chromatography of the gastrin released was not carried out in our study, the molecular species is unknown (Berson and Yalow, 1971), and this must remain conjecture.

There is a positive correlation between the elevated levels of circulating gastrin and the acid production in response to an oxo-meat extract stimulation at 2 to 3 months following PCV, but acid secretion in response to a variety of stimuli appears to be reduced and parietal cell responsiveness is a fraction of what it was previous to operation. After both operations, the gastrin response to meat extract stimulation is the same in insulin positive and insulin negative patients (Table 1). Only in the 3 insulin negative patients after SV + P is there no acid response to meat extract stimulation, with a positive acid response in the insulin positive patients. However, the number of patients is too small to draw any conclusions.

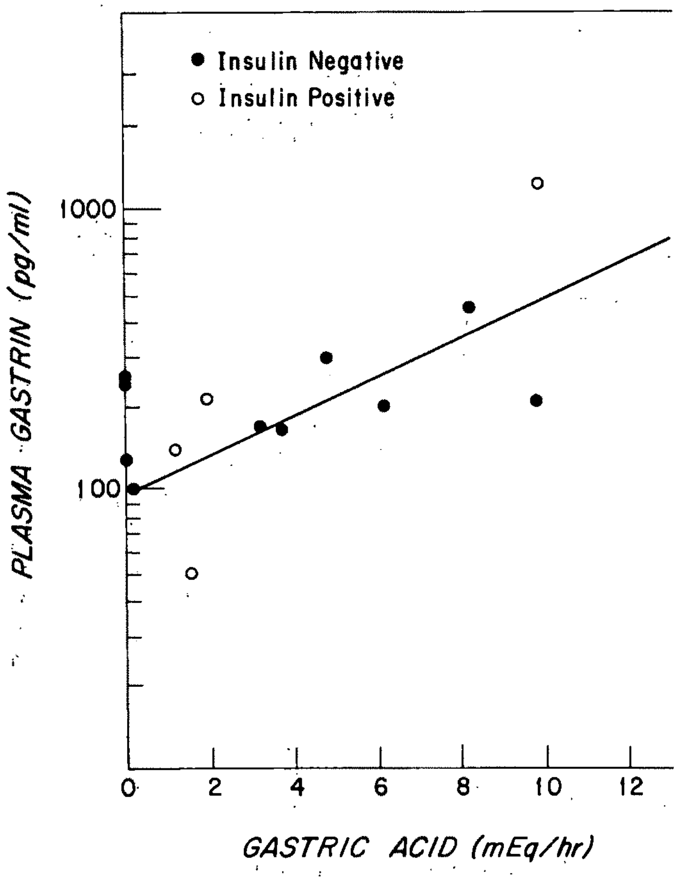

FIG. 6. Relationship between meat extract stimulated plasma gastrin levels (peak response) and gastric acid response in a group of patients who had undergone parietal cell vagotomy. There is no difference between the insulin positive and insulin negative patients, and a correlation coefficient of 0.62 is apparent, yielding a slope significantly different from zero at the P = 0.05 level.

After PCV, the meat extract stimulated acid secretion is not separable on the basis of insulin positivity or insulin negativity, a finding of potential importance, since the number of insulin positive patients appears to increase in time and may exceed 50% at times greater than one year following parietal cell vagotomy.[5] It also suggests that the release of gastrin after meat extract stimulation is more important than vagal innervation for the stimulation of gastric acid secretion.

A recent demonstration of reinnervation of the parietal cells at periods of time of greater than a year following parietal cell vagotomy with an associated increase in peak acid output following pentagastrin stimulation[5] makes one wonder whether in fact continued conversion of patients from insulin negative to insulin positive will not yield an increased acid secretion close to that of the preoperative levels. (The most recently available figures suggest a close to 70% positive Hollander Test at the end of 2 years. Acid secretory capacity is about 60–70% preoperative capacity. D. Johnston and J. C. Goligher, personal communication.)

Despite indications that the acid relieving benefits of parietal cell vagotomy may be temporary, and that increased parietal cell responsiveness combined with increased circulating basal and stimulated gastrin may lead to increased acid production, the early clinical results continue to be excellent. It should be noted, however, that similar enthusiasm followed the introduction of posterior gastrojejunostomy, and that the mean time of recurrence which, ultimately, was as high as 30%, was approximately 13 years after the performance of the initial procedure.[37] Moreover, the patients with normal duodena operated on in most of these series appear to be a group of patients at an earlier stage of their disease than those patients with scarred duodena generally operated on in the United States. While it is impossible to predict the effects of stage of disease upon time of recurrence, it would be logical to assume that those patients at an earlier stage in the peptic ulcer disease perhaps might recur at a later date and form a more favorable group for early operation. Thus, although the data reported here and in other series give cause for concern, the prospective trials now in progress in a variety of centers appear to be well justified, since the benefits of this operation as far as preservation of normal physiology and gastric emptying and possible late nutritional effects may be important.

Finally, these experiments demonstrate that in man the primary determinant of gastric acid secretion appears to be parietal cell responsiveness, and that in spite of the release of large quantities of presumably potent antral gastrin, both in the basal state and in response to food, acid production is not increased in these patients. Although a correlation may be demonstrated between gastrin and acid secretion, the dose response curve is shifted far to the right with a denervated parietal cell mass.

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A Controlled Surgical Approach to Annulo-aortic Ectasia

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Annulo-aortic ectasia has attracted much surgical attention in the last 20 years. Replacement of the aortic valve and ascending aorta from the valve ring to just proximal to the innominate artery eliminates most, if not all, the pathologically involved tissue. Composite valve-Dacron tube grafting, plus elective saphenous vein grafts from the coronary orifices to the Dacron tube or distal aortic wall, provide a safe systematic approach to this entity. A review of surgical techniques and a description of a successful case employing this method are presented.

ANEURYSM of the ascending aorta co-exists frequently with aortic valvular insufficiency. This pathologic complex appears to be related to an intrinsic weakness of the aortic valve ring and ascending aortic wall.[15] Cystic medial necrosis is the most frequent histologic finding in the affected areas.[1] Clinically, these lesions are often associated with Marfan's syndrome in its full-blown picture[16] or as part of its many variants or formes frustes.[10]

The physiologic consequences of annulo-aortic ectasia, as Ellis and Cooley[8] called this combination of anatomical findings, involve progressive dilatation of the aortic ring and ascending aorta to a point proximal to the origin of the innominate artery. The affected segment takes on the configuration of a pear or a Florence flask. As the aortic root expands, the orifices of the coronary arteries are separated from the valve structures and the aortic sinuses, and are often found several centimeters above the commissural level. Dilatation of the aortic ring prevents approximation of the valve leaflets during diastole with the production of varying degrees of aortic insufficiency. Other mechanisms of valvular incompetence include direct involvement of the cusps in the myxomatous process[20] and acute prolapse of one or more cusps during aortic wall dissection. Increased pulse pressure caused by the valvular insufficiency undoubtedly transmits more powerful volume thrusts to the already-weakened ascending aortic wall, thus establishing a vicious perpetuating cycle.

Intimal tears of the ascending aorta and aortic dissections[14] are not infrequent with their attendant dangers of rupture, occlusion of important aortic branches, and catastrophic aggravation of valvular incompetence. Understandably, the well developed and untreated syndrome is highly lethal.

The elucidation of the mechanical factors involved has prompted surgeons to attempt their correction. A number of operative approaches have been employed during the past 20 years with varying degrees of success.

In 1956, Bahnson and Nelson[2] initiated surgical efforts at arresting the devolutionary course of this lesion when he resected varying amounts of anterolateral ascending aortic wall employing a special clamp of his own design. He followed excision with wrapping of the reconstituted vessel with a nylon cloth "scultetus binder" from a point distal to the coronary ostia to the most distal point of excision. Although he reported palliation in three survivors out of four such attempts, two of these died within five months of surgery and in the remaining patient the murmur of aortic insufficiency persisted.

In 1960, Bahnson and Spencer[3] reported on the excision of the aneurysmal segment of the ascending aorta with replacement by a woven Teflon prosthesis during cardiopulmonary bypass and intraoperative coronary perfusion. It was their belief that such a procedure would indirectly benefit the valvular insufficiency. Three survivors out of four patients operated upon were reported as improved for periods up to 18 months after the operation.

In the same year Muller et al.,[18] using a similar technique with extracorporeal pump oxygenator support,

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replaced the supravalvular aorta from a point just distal to the coronary ostia to a point proximal to the innominate artery and concomitantly corrected the valvular insufficiency by bicuspidization of the valve, a technique originally described by Garamella.[9] The following year Ellis, Cooley and DeBakey[8] excised the affected ascending aortic segment, bicuspidized the aortic valve and were able to anastomose the aortic ends together without benefit of an interposed prosthetic tube.

Impressed by the dilated and histologically involved aortic wall remnant from the ring level to that of usual transection, Wheat[23] in 1964, reported on a technique and successful case where wall resection was carried down proximally to the aortic ring except for two small tongues of aortic wall containing the coronary ostia, which were then sutured to the proximal tailored end of the woven Teflon aortic graft. The aortic valve was replaced with a Starr-Edwards ball valve prosthesis. His patient was alive and well 13 months after surgery. By 1971, Wheat and his co-workers[22] had operated in similar fashion on 13 patients. There were two operative deaths. Among the postoperative complications, bleeding was prominent in 5 and 2 of these required re-operation because of tamponade. In addition, 7 of the 11 survivors died between one month and 5 years postoperatively from a variety of causes. The longest followup was in a patient who died 5 years after the initial procedure, at reoperation for ball variance in the implanted Starr-Edwards prosthesis.

Throughout the 1960's many others published their surgical results on a growing population of patients affected with this aortic root complex. Certain general principles became established: the valvular insufficiency should be corrected by bicuspidization or by replacement with prosthetic valves[5] or homografts.[17] The dilated segment of the ascending aorta distal to the coronary ostia was usually replaced with a suitable plastic cloth tube or by direct anastomosis of the aortic cut ends.[21] Modifications in technique suggested the difficulties encountered in suturing the friable tissues (ring, aortic wall) of many of these patients, especially if recent dissection had occurred. Concern was also expressed about the fate of the aortic root remnant in those patients where proximal aortic transection had been made just distal to the coronary ostia and to whether this area of the sinuses of Valsalva might not undergo further postsurgical dilatation.

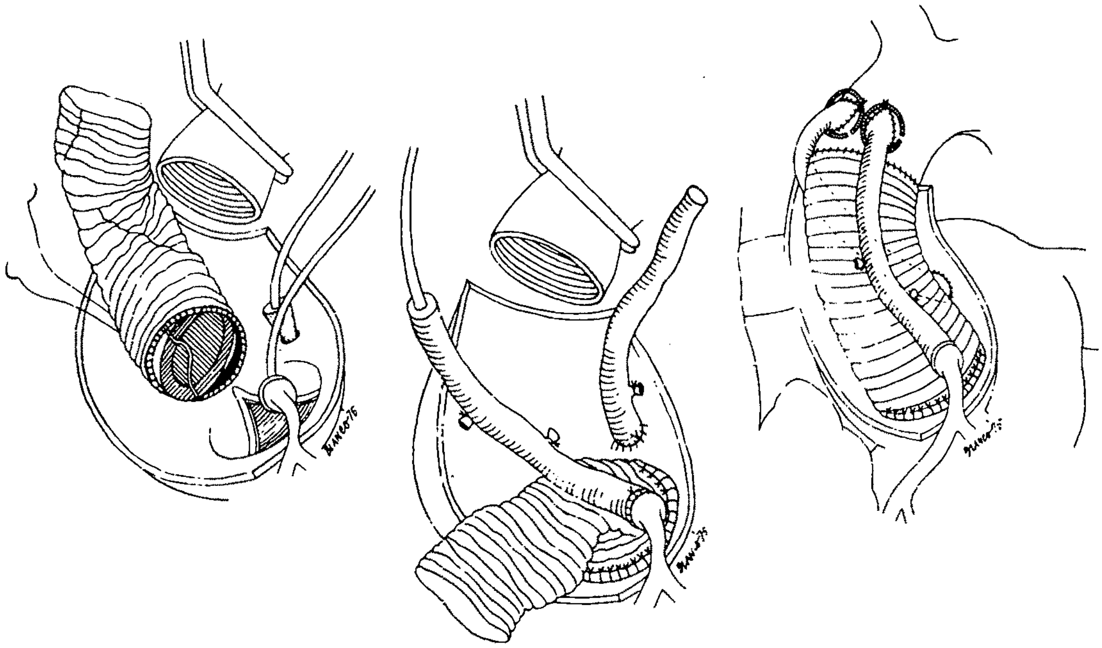
Groves[11] was prompted to suggest that in those patients where the coronary ostia had been incorporated in the dilated proximal portion of the aneurysm it might be well to consider detaching them with a surrounding aortic cuff and reanastomosing this cuff to a graft which could then be attached more proximally to the valve ring.

In 1968, Bentall and DeBono[4] published their experience with just such a method. In a 33-year-old patient with annulo-aortic ectasia they replaced the entire ascending aorta and the aortic valve with a composite graft made up of a ball valve prosthesis and a woven Dacron tube. The artificial valve was incorporated in the proximal end of the tube graft and implanted in the valve ring after excision of the valve cusps. The coronary ostia were then sutured to holes made on the graft at appropriate distances above the valve level. This appeared to deal effectively with the problem of postoperative dilatation of the aortic root and to some extent with the problem of proximal anastomosis to the friable and pathologically affected remaining tissues of this area.

Helseth and co-workers[12,13] have employed this method with some variations and attest to its efficacy in dealing with these problems.

On October 25, 1974, we had the opportunity to employ this technique on a 26-year-old man with the anatomico-pathologic picture described above. Although the diagnosis of aortic valve insufficiency and ascending aortic dilatation was made preoperatively, an unexpected finding at operation was an aortic dissection extending from a point just distal to the coronary arteries to areas beyond the operative field (autopsy revealed the dissection to involve the aorta beyond the renal arteries). Composite grafting of the valve and ascending aorta with direct suture implantation of the coronary ostia to the Dacron graft was carried out during cardiopulmonary bypass and we were impressed with the ease of this approach over methods employed previously. However, we were unpleasantly surprised by the appearance of significant bleeding from the posterior (left) coronary-graft anastomosis upon release of the aortic cross clamp. Undoubtedly the increased tissue friability attendant on the aortic wall dissection contributed to this phenomenon. Attempts to deal with the hemorrhage proved unsuccessful because of the inaccessibility of the bleeding area behind the now-distended aortic graft. Cardiopulmonary bypass was re-established and after aortic cross-clamping and decompression of the graft segment, the coronary anastomoses were taken down. Saphenous vein segments were then obtained, reversed and anastomosed to the coronary ostia which together with a small rim of aortic wall had been detached from the wall of the aneurysm. Perfusion with coronary catheters through the vein grafts attested to the water-tight nature of the distal anastomoses before the proximal ends were sutured to appropriate holes in the woven Dacron tube.

After the second release of the aortic cross clamp, anastomotic bleeding was minimal but a prolonged bypass time and possibly other factors precipitated uncontrol-



FIGS. 1 to 3. (left) The anterior wall of the aneurysm and the aortic valve have been resected. The right coronary ostium is free and coronary perfusion is maintained throughout. The composite graft is implanted proximally into the aortic ring. (center) Saphenous vein segments are reversed and anastomosed to the free right coronary ostium and the margin of the left coronary ostium. Perfusion through the vein grafts permits the surgeon to check for anastomotic leaks and correct them at this stage. (right) The distal aortic anastomosis is finished and the free ends of the vein segments are anastomosed to the Dacron tube or the distal aorta. Markers are in place around the aortic vein anastomoses to facilitate visualization during postoperative studies.

lable arrythmias in the immediate postoperative period. The patient died eight hours after operation without having regained consciousness.

This experience impressed us with the systematic soundness of our second approach and we decided to employ it electively on future patients with this condition.

Case Report

A 32-year-old Negro man was admitted to Hahnemann Hospital on December 26, 1974. He had been in good health until 8 months previously when he started noticing shortness of breath while lying down. He soon developed three pillow orthopnea, paroxysmal nocturnal dyspnea, night sweats and occasional hemoptysis for which was was hospitalized elsewhere in August of 1974. A heart murmur was detected at this time and he was placed on Digitalis and diuretics. Since discharge he had noticed increasing dyspnea on exertion. There was no history of rheumatic fever but he had been told that he had high blood pressure during the past 10 years. In recent months he had experienced a sensation of "pins and needles" in the anterior chest and this was relieved by rest.

On physical examination he did not show any stigmata of Marfan's syndrome. He was tall but muscular. Heart rate was 96 per minute and regular. Blood pressure was 150/40. Respirations 16 per minute. All peripheral pulses were present and bounding. There was gross cardiomegaly on palpation, with the apical impulse in the 6th interspace just lateral to the mid-clavicular line. A systolic thrill was felt over the second interspace to the rightr of the sternum and a harsh Grade IV/VI ejection systolic murmur was heard over this area. A_2 was not heard and a Grade II/VI diastolic decrescendo murmur was evident along the left sternal border. The rest of the examination was non-contributory.

Cardiac catheterization and ventriculography performed on December 30, 1974, revealed a dilated, poorly contracting left ventricle with an end diastolic pressure of 40 mmHg. There was a 4+ aortic insufficiency through a tricuspid aortic valve. The ascending aorta was markedly dilated. Pulmonary artery pressure was 50/32. Cardiac output was calculated at 4.96L/min.

A diagnosis of severe aortic insufficiency with possible annuloaortic ectasia was made and the patient scheduled for corrective surgery which was thought to be associated with a high risk in view of his poor left ventricular function.

Method

On January 10, 1975, the chest was entered through a mid-sternal incision. There was gross cardiomegaly affecting all chambers but especially the left ventricle. There was a prominent systolic and a softer diastolic thrill over the aortic area. The ring and immediate ascending aorta were markedly dilated and at a point 3cm above the valve level the vessel was 10cm in diameter, tapering gradually to a point about 4cm proximal to the origin of the innominate artery where a normal caliber (approximately 3cm in diameter) was resumed. The affected segment was covered with dilated adventitial capillaries except for yellowish thinned-out areas that appeared on the verge of rupture.

After institution of cardiopulmonary bypass, a cross clamp was applied just proximal to the origin of the innominate artery and the aneurysm was entered. The orifices of the coronary arteries were seen to arise from the aneurysmal sac about 4cm above the valvular level. They were cannulated individually and mildly hypothermic coronary perfusion maintained thereafter. The aortic ring was markedly dilated and gross central insufficiency resulted from lack of coaptation of the aortic cusps. These were excised, as well as the anterolateral wall of the aneurysm from the ring to a point 3cm from the aortic cross clamp. The right coronary ostium and a 3mm circumference of aortic wall were detached completely from the sac. The left coronary ostium was left in situ in the posterior wall of the aneurysm.

The aortic valve and ascending aorta were then replaced by a composite graft of woven Dacron (30mm) with a #29 tilting disc Bjork-Shiley prosthesis previously sutured to its proximal end. The proximal graft-valve implantation was made with closely spaced 3-0 Tevdek sutures into the remaining aortic valve ring. During these maneuvers coronary perfusion was maintained through special catheters (Fig. 1)

Saphenous vein segments were obtained, reversed and their proximal ends anastomosed end-to-end to the detached right coronary ostium and to the periphery of the undisturbed left coronary orifice with continuous 6-0 Proline, after which coronary perfusion was resumed by placing the catheter tips in the free ends of the saphenous grafts. The anastomoses were inspected and any small leaks corrected with further interrupted sutures of 6-0 Proline (Fig. 2).

3-0 Tevdek was employed in continuous fashion for the distal anastomosis. After the release of the distal cross clamp and when no significant bleeding had ensued, the saphenous vein segments were found to be long enough to be anastomosed directly to the normal-appearing aorta between the distal graft anastomosis and the beginning of the arch, and this was done using exclusion clamps in the manner employed routinely during coronary bypass surgery. The left coronary graft was placed posterior to the Dacron tube and anastomosed to the right lateral aortic wall. The right vein graft was anastomosed anteriorly (Fig. 3). (They could have been anastomosed just as easily to accessible areas of the Dacron graft.)

The rest of the procedure was uneventful as was the postoperative period. On January 29, 1975, a repeat cardiac catheterization revealed pulmonary artery pressures of 26/12 with a cardiac output of 7.57L/min. The prosthetic Bjork-Shiley aortic valve was in place and functioning well. The prosthetic segment of the aorta was well visualized. Both vein grafts as well as the coronary arteries were also well visualized throughout their extent. It was felt that the patient's hemodynamics had improved significantly from those of the preoperative study. He was discharged on January 31, 1975.

Comment. Since the inception of surgical attempts for the correction of annulo-aortic ectasia, efforts have been directed at eliminating valvular insufficiency and replacing progressively longer segments of the affected ascending aorta. The techniques of composite grafting described independently by Bentall and DeBono[4] and by Edwards and Kerr[7] satisfied the need for total replacement of the ascending aorta and the aortic valve. Their method of suturing the coronary ostia directly to the prosthetic tube graft leaves the possibility of catastrophic bleeding occurring at operation, as in our first case, or even long after operation as occurred in one of the patients reported by Crosby et al.[6] The use of a saphenous vein segment for atherosclerotic coronary bypass grafting in association with replacement of the aorta above the coronary ostia, and replacement of the aortic valve was reported by Najafi in 1973.[19] Its employment as a planned step in surgery for annulo-aortic ectasia appeals to us for three reasons: it facilitates a more accurate and tension-free anastomosis to the origin of the coronary arteries whether the latter are dissected free or not. It permits constant perfusion of the coronary arterial tree while other steps in the procedure are carried out, and more importantly, it allows the surgeon to test the suture lines under physiologic pressures and avoid unexpected and inaccessible bleeding at the time of release of the aortic cross clamp.

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Aspiration Pneumonia:

Experimental Evaluation of Albumin and Steroid Therapy

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An experimental model using an ex vivo perfused ventilated canine pulmonary lobe was used to study aspiration pneumonia. After intrabronchial acid instillation, the lobe weight tripled, air way pressure and pulmonary artery pressure doubled, and intrapulmonary shunting increased from 5.5% to 53.4%. If large quantities of albumin were added to the lobe perfusate 5 minutes after intrabronchial acid instillation, weight gain, air way and pulmonary artery pressure, and intrapulmonary shunting were unchanged from control levels. If large quantities of steroid were added to the lobe perfusate 5 minutes after intrabronchial acid instillation, the lobe weight doubled but air way pressure and pulmonary artery pressure, and intrapulmonary shunting were not significantly different from control values. It is surmised that intrapulmonary acid aspiration causes an immediate and marked change in pulmonary capillary permeability. Albumin administration by counteracting this permeability change, and steroid administration by modifying the permeability change, are both beneficial following acid aspiration.

ASPIRATION of gastric contents into the tracheobronchial tree occurs during a wide variety of clinical situations.[4] When the aspiration is massive, it is associated with a mortality as high as 60%.[1,6] Although many recommendations for therapy have been made, clinical treatment remains largely supportive and difficult to evaluate. In an effort to study direct pulmonary response to acid injury and modification of the injury by therapy, the ex vivo perfused ventilated canine pulmonary lobe model was used. Using this model, the direct pulmonary response to acid aspiration and its modification by two of the current means by which aspiration pneumonia is treated, steroid and albumin administration, were evaluated.

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Experimental Preparation

Through a lateral thoracotomy incision the canine left lower lobe was exposed and the hilar structures dissected free. The dog was then anticoagulated with heparin (2mg/kg body weight). A cannula was inserted into the pulmonary artery to the left lower lobe taking care to avoid air in the arterial side of the circuit. The pulmonary vein from the left lower lobe was then cannulated through the left auricular appendage. The dog was exanguinated and the 800 ml of blood obtained were used to prime the perfusion system. The bronchus was cannulated last and the lobe removed. Using methylcyanoacrylate monomer 4 patches were attached to the pleural surfaces of the lobe and from these patches the lobe was suspended from a weight transducer with the hilar structures in a dependent position. All lobes were ventilated with a Harvard piston-type respirator using 100% oxygen at a rate of 16 per minute. Tidal volume was approximately 2 ml/gm of lobe weight. End expiratory pressure was maintained at 5 cm of water. Venous drainage was collected in a reservoir and returned to a Bentley Q-130 infant size oxygenator. A gas mixture of 95% nitrogen and 5% carbon dioxide was used to deoxygenate the blood. The lobe was perfused with the deoxygenated blood using a Sarns roller pump (Fig. 1). The flow rate was increased slowly until the pulmonary artery pressure reached 15 mm/Hg. Thereafter the flow was kept constant. Flow rates generally were in the range of 80 to 90 ml per minute.* By

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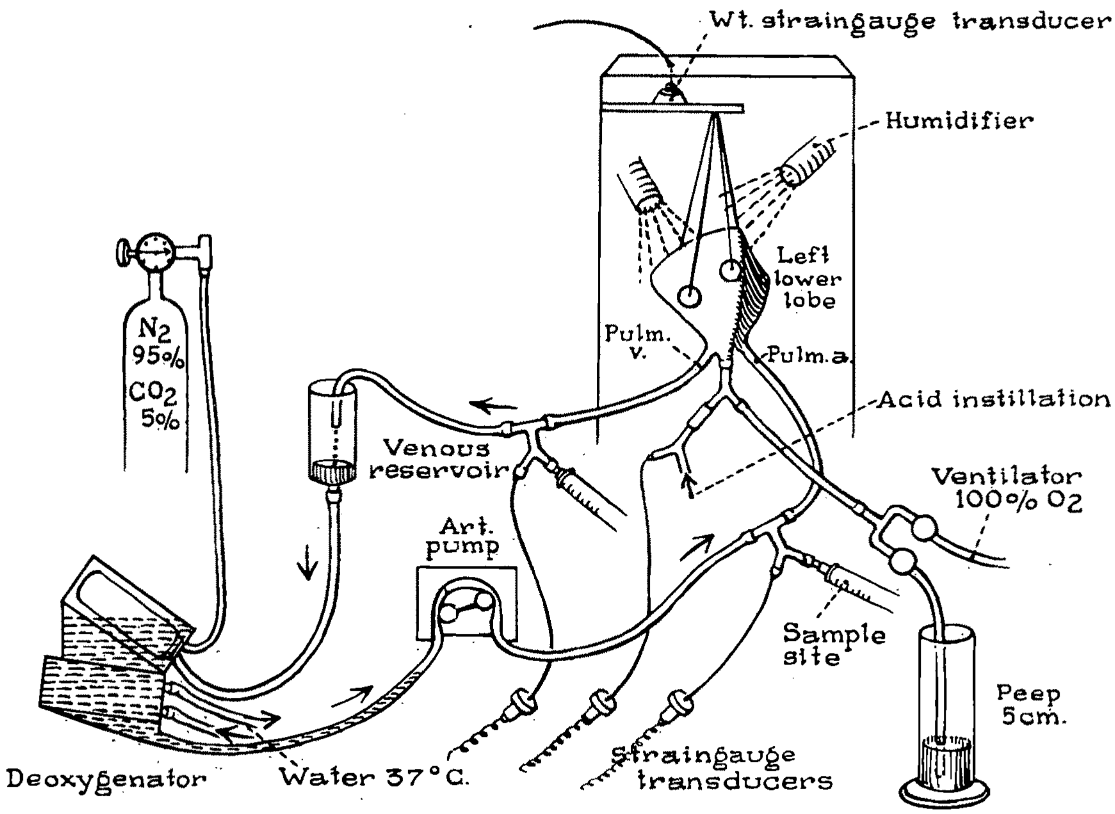


FIG. 1. Experimental preparation using ex vivo, perfused, ventilated canine left lower lobe.

adjusting the height of the venous reservoir, venous pressure was kept at 0 to −2 mm/Hg. Pulmonary artery, venous, and airway pressures and lobe weight were monitored continuously with Statham p23 Db transducers and recorded with an Electronics for Medicine multiple channel recorder. The temperature of the perfusate was maintained at 37° ± 1 C and the lobe was kept in a heated humidified hood to maintain normal temperature and humidity. Arterial and venous blood samples were analyzed periodically for pH, Po_2, and Pco_2 with a Corning blood gas analyzer. Arterial samples were also used for hematocrit and hemoglobin determinations. Intrapulmonary shunting was determined with the use of the standard shunt formula.[17] Sodium bicarbonate was added periodically to the perfusate to maintain normal acid-base balance.

Protocol

All lobes were perfused for at least 45 minutes to allow them to stabilize and then were placed into one of four groups.

Group I: *Saline Control* (*4 lobes*). After stabilization 0.018 ml/gm of lobe weight of saline was introduced into the lobar bronchus by means of a nebulizer. Recordings were made at 15 minutes, 30 minutes and thereafter at 30 minute intervals of PA pressure, venous pressure, air way pressure and lobe weight. Samples of arterial and venous blood were drawn at 30 minute intervals for calculations of shunt. The perfusion was continued for four and one half hours.

Group II: *Hydrochloric Acid Control* (*8 lobes*). After stabilization 0.018 ml/gm of lobe weight of 0.1 N hydrochloric acid was introduced into the lobar bronchus by a means of a nebulizer. All parameters were followed as in Group I and the perfusion was continued for 4.5 hours.

Group III: *Hydrochloric Acid Albumin Treatment* (*8 lobes*). These lobes were handled identically to group II except that five minutes after the acid was instilled, 37.5 gm of concentrated human salt-poor albumin was added to the perfusate.

Group IV: *Hydrochloric Acid Steroid Treatment* (*8 lobes*). These lobes were handled identically to group II except that 5 minutes after the acid was instilled methylprednisolone sodium succinate (Solu-Medrol) 40 mg/kg donor dog weight was added to the perfusate.

At the end of the study static compliance of the lobe was determined by a standard pressure-volume deflation curve method.[13] After formalin fixation, the nonperfused left upper lobe of the dog and the perfused left lower lobe were grossly examined. The lobes were cut at 5 mm intervals in search of focal lesions. Blocks were selected to show the hilar structures and the peripheral pulmonary parenchyma as well as any focal lesions noted. These blocks were processed into paraffin and sections were cut and stained with hematoxylin and

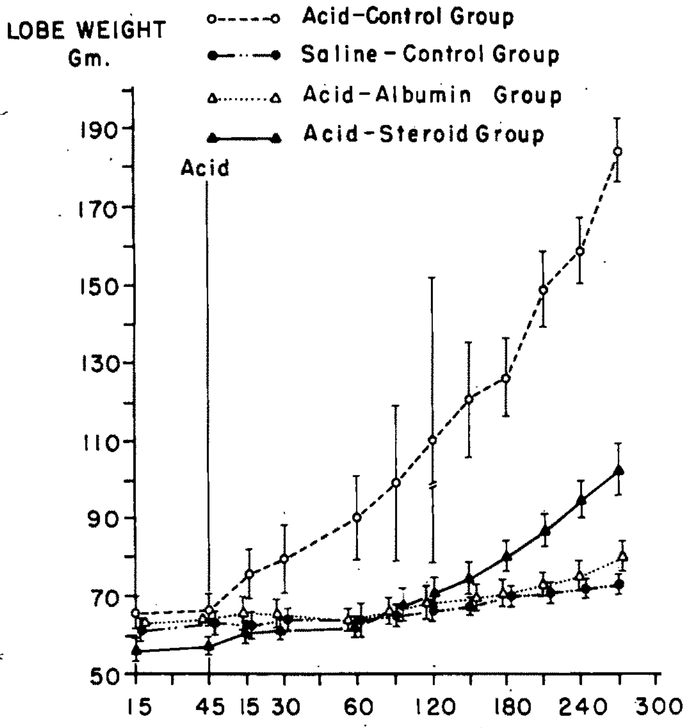


FIG. 2. Changes in lobe weight in control and treated groups following aspiration. Values are presented as the Mean ± 1 S.E.

eosin. The slides were then evaluated without prior knowledge of which of the 4 groups to which the specimen belonged. These were then correlated with the insult and treatment. All the results of this study were subjected to statistical analysis by the Student's *t* test.

Results

Group I: Saline Control. In this group the weight of the isolated lobes remained relatively constant throughout the 4.5 hour perfusion (Fig. 2). Mean pulmonary artery pressure dropped 15% during the first hour and then stabilized (Fig. 3). Airway pressure increased minimally during the 4.5 hour period (Fig. 4). Intrapulmonary shunting remained minimal throughout the entire perfusion (Fig. 5): The lobes grossly appeared normal during the perfusion period. The pressure volume deflation curves were within the normal range (Fig. 6).

Group II: Acid Control. Within seconds following the instillation of acid, scattered patches of discoloration could be seen on the pleural surface of the lobes. These gradually enlarged and were surrounded by hemorrhage. These lobes rapidly and steadily gained weight during the perfusion (Fig. 2). Five of the 8 lobes developed massive pulmonary edema 3.5 hours after the perfusion began, and the runs were terminated. Only three lobes completed the planned 4.5 hours of perfusion. A marked increase in airway pressure (Fig. 4) and mean pulmonary artery pressure (Fig. 3) occurred.

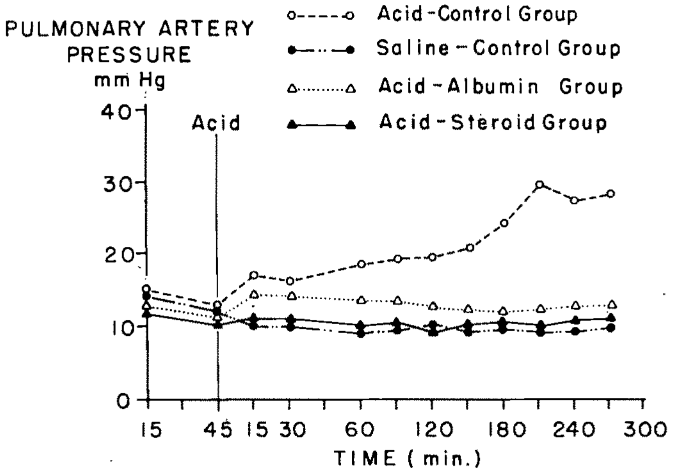


FIG. 3. Changes in pulmonary artery pressure in control and treated groups following aspiration.

Marked intrapulmonary shunting developed in all lobes (Fig. 5). At the end of the study the lobes appeared edematous and consolidated, with scattered hemorrhagic areas. The pressure-volume deflation curves were markedly depressed (Fig. 6).

Group III: Acid Albumin Treatment. The massive weight gain seen in Group II was almost completely eliminated in this group by adding albumin (Fig. 2). Thirty minutes after acid instillation, the initially increased weight that followed aspiration had declined to pre-aspiration level and it was maintained at this level until one and one-half hours. The weight then increased minimally during the rest of the perfusion. The weight gain was not statistically different from that seen in the control lobes receiving saline. Intrapulmonary shunting increased minimally (Fig. 5). Pulmonary artery and airway pressure were not significantly increased (Figs. 3 and 4).

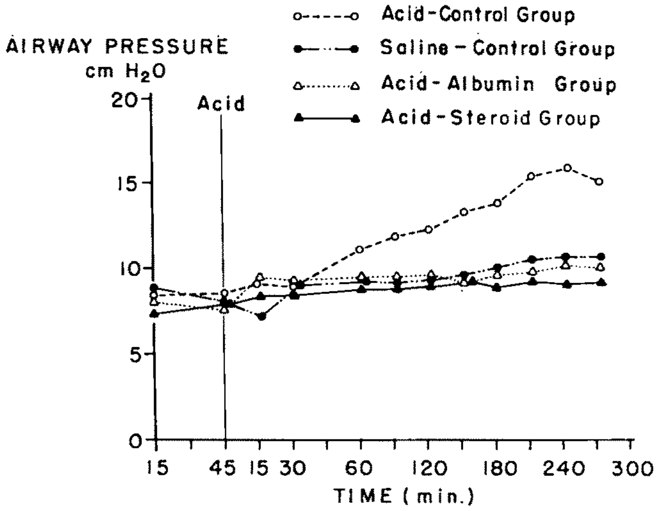


FIG. 4. Changes in airway pressures in control and treated groups following aspiration.

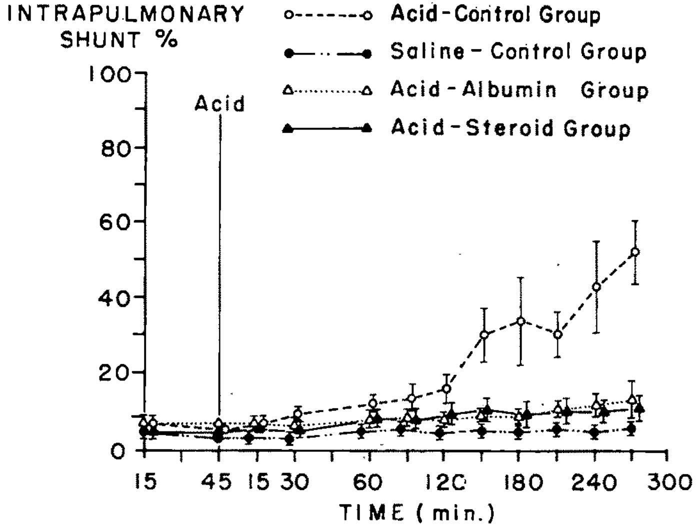


FIG. 5. Changes in intrapulmonary shunting in control and treated groups following aspiration. Values are presented as the mean ± S.E.

None of the lobes showed evidence of pulmonary edema, and at the end of the perfusion they appeared grossly normal. Albumin concentration in the perfusate averaged 2.8 gm% prior to albumin administration and 9.3 gm% after. The pressure-volume deflation curves were only slightly depressed as compared to the saline control group, but were significantly better than the acid group.

Group IV: Acid Steroid Treatment. The lobes in this group demonstrated a moderate weight gain. The weight gain, however, was statistically not different from the saline group until the third hour after acid instillation. The total weight gain was, nonetheless, significantly less than the acid group receiving no treatment. Pulmonary artery, air way pressure, and intrapulmonary shunting demonstrated only slight increases that were not statistically different from the saline control group (Figs. 3 to 5). At the end of the perfusion period, the lobes appeared grossly normal and the pressure-volume deflation curves were depressed less than in the acid-control group (Fig. 6).

Histology

The nonperfused upper lobes of all animals were histologically normal except for occasional patches of bronchopneumonia. A cuff of edema fluid and/or hemorrhage was evident around the large and medium size vessels in the perfused lobes of all four groups. In Group I (Saline Control) lobes, there were, in addition, occasional small areas of intra-alveolar edema fluid accumulation. The most impressive change noted in the Group II lobes (Acid Control) was a massive and diffuse collection of edema fluid and blood in the alveolar spaces (Fig. 7). These changes were essentially reversed to Saline Control (Group I) levels by the addition of albumin (Group III) to the perfusate. The addition of steroids (Group IV) to the perfusate resulted in a marked decrease of the hemorrhage in the alveolar spaces but produced no discernible decrease in the amount of edema fluid histologically evident in the alveolar spaces.

Although the alveolar capillary bed was almost certainly the source of the hemorrhage and edema fluid in the alveolar spaces, the only changes noted in the alveolar wall were congestion and dilation of the capillaries. This was noted in all 4 groups of perfused lobes. Edema was not evident in the alveolar walls themselves. It is perhaps not surprising that in view of the acute nature of the injury and the absence of a source of a cellular response thereto, that there was little accumulation of fluid between the capillary wall and the pneumocytes which lines the alveolar space.

Discussion

The physiologic response following massive aspiration of gastric contents is rapid in onset, marked in degree, and varied in extent. Early respiratory insufficiency from intrapulmonary shunting is frequently seen following massive aspiration. This is thought to be secondary to surfactant destruction with wide spread areas of atelectasis.[11] The clinical picture of pulmonary edema can also be seen following massive aspiration. This initially was thought secondary to acute heart failure. More recently massive extravasation of fluid from injured capillaries into the alveolar spaces in the presence of normal left heart pressures has been identified as the patho-

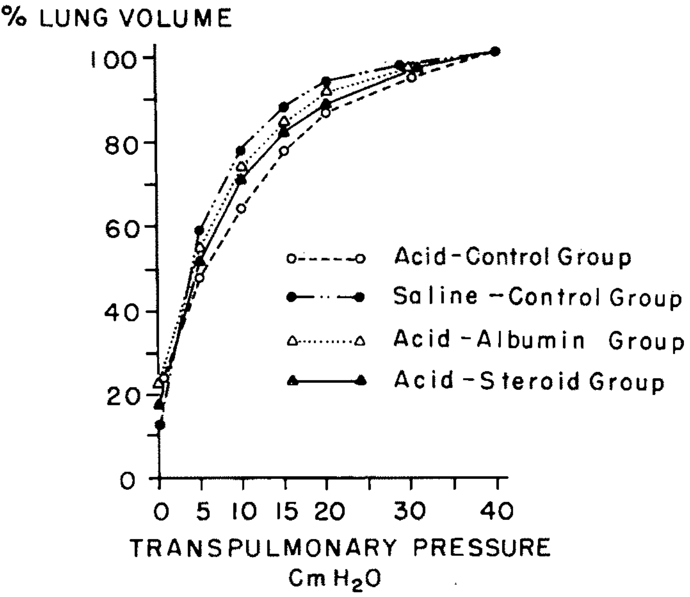
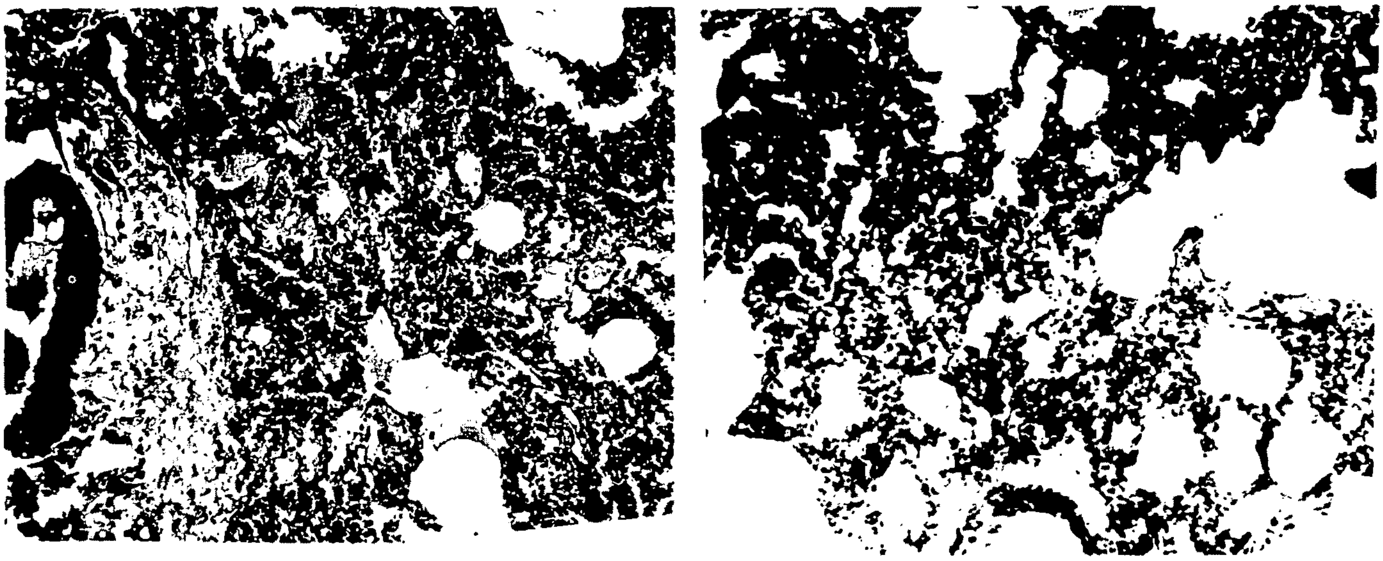


FIG. 6. Pressure-Volume deflation curves performed 4½ hours after perfusion in control and treated groups following aspiration.



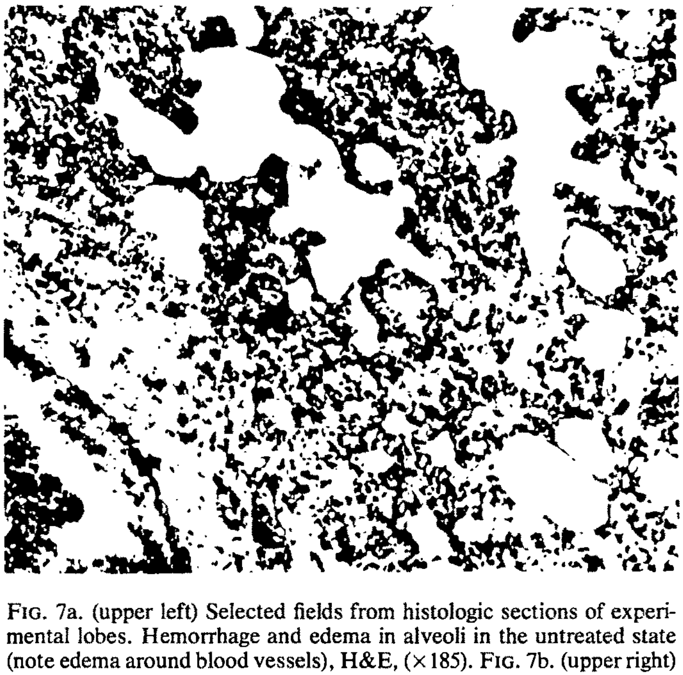


FIG. 7a. (upper left) Selected fields from histologic sections of experimental lobes. Hemorrhage and edema in alveoli in the untreated state (note edema around blood vessels), H&E, (×185). FIG. 7b. (upper right) Diminution of both hemorrhage and edema in alveoli seen with albumin administration, H&E, ×185. FIG. 7c. (lower right) Decrease in hemorrhage but not edema (note edema blood vessel) in lobe treated with steroid, H&E, ×185.

genetic mechanism.[1,11] Finally, systemic hypotension secondary to massive extracellular fluid loss into injured pulmonary tissue can be seen both experimentally[1] and clinically[18] following aspiration. This complex clinical syndrome that follows massive aspiration of gastric contents has proven refractory to most supportive care, and mortality rates in the range of 60% to 80%[1,6] have been reported.

In recent years a great deal of investigative work using experimental animal models has been carried out to evaluate treatment modalities in aspiration pneumonia. Results have been conflicting and difficult to assess. Even data evaluating systemic steroid therapy, the cornerstone of treatment for this disorder for the past 20 years, are contradictory and no consensus of its value can be gained from a review.[2,3,7-9,11,12,14,15,20] For this reason, the ex vivo perfused, ventilated canine lobe was chosen as a model with which to evaluate the pulmonary response to acid injury, and its modification by various treatment parameters in the absence of other adaptive systemic responses.

Weight, pulmonary artery, and airway pressure remained stable and in a normal physiologic range in all saline control lobes. In contrast, following the intrabronchial instillation of hydrochloric acid massive weight gain occurred, pulmonary artery and airway pressures doubled, and 5 of the 8 lobes developed pulmonary edema which necessitated termination of the perfusion. In addition, intrapulmonary shunting increased from 6% to over 50%. Intrapulmonary shunting did not surpass 20%, however, until three hours after the acid insult suggesting that it was more related to edema and massive weight gain than an immediate sequela of acid injury, such as surfactant destruction and atelectasis. Histologically, massive accumulation of hemorrhagic fluid in the alveolar spaces was the most striking finding. An immediate change in capillary permeability with subsequent extracellular fluid loss is probably the most significant pathologic event following acid aspiration. Intrapulmonary shunting and hypoxia, a decrease in pulmonary compliance with an increase in air way pressure could all be secondary to the massive filling of the alveolar spaces with extracellular fluid.

The addition of massive quantities of albumin to the perfusate 5 minutes after acid injury reversed all the physiologic changes seen in the untreated acid lobes. This supports the thesis that a permeability change in pulmonary capillaries is the major pathologic injury from acid aspiration, and is responsible for the subsequent physiologic response. The lobe weight increased slightly following acid instillation, and then actually decreased following albumin administration until two hours of perfusion had elapsed. The slight weight gain recorded by the end of the perfusion period was not statistically significantly increased over those control lobes receiving no acid. The remaining physiologic parameters were also not significantly different from the control lobes receiving saline. The quantity of albumin used in this study increased serum values from 2.8 gm% to 9.3 gm%, a level that would not be tolerated clinically. There is no reason to believe that its effect isn't graded, however, and that a lower dose, while not completely reducing the physiologic response to acid injury, would certainly modify it. Albumin administration as a means of decreasing pulmonary interstitial and alveolar edema has been found effective in other clinical settings,[19] and its use in aspiration pneumonia should be given a clinical trial.

The role of steroid therapy in the treatment of aspiration pneumonia is controversial. Despite universal clinical use, mortality rates have remained unacceptably high. Experimental studies have also been contradictory with some studies showing benefit[2,3,8,14,16] and others showing no benefit.[1,7,9,10] The data from the present study clearly show steroid administration to be of benefit, although it was not as effective as albumin in reversing the physiologic response to acid injury. Weight gain occurred in the steroid treatment group but it was only one-half as much as seen in the untreated acid controls. Intrapulmonary shunting, and pulmonary artery and air way pressures remained normal, however, and were not significantly different from the control lobes receiving saline. This again suggests that the elevation of these physiologic parameters in the acid control lobes was secondary to massive pulmonary edema. Presumably, by modifying the permeability change in the pulmonary capillaries secondary to the acid insult, steroid therapy prevented massive edema, although a moderate weight gain did occur. Since massive weight gain was prevented, the sequela of a decrease in pulmonary compliance, an increase in pulmonary artery pressure, and an increase in intrapulmonary shunting were not seen.

The mode of action of albumin and steroids in modifying the response to aspiration pneumonia would appear to be different. Albumin acts as an osmotically active agent to counteract changes in capillary permeability, but probably has no direct effect on the injury itself. In contrast, steroids presumably modify the capillary permeability changes caused by the acid injury. One could thus reasonably expect the use of both agents together to be additive. We would, therefore, continue to recommend massive steroid administration following aspiration of gastric contents. In addition, the administration of as much albumin as the patient's cardiovascular system will allow should be carried out. Through this regimen, one would hope to counteract and modify capillary permeability changes and avoid the massive pulmonary edema which appears to be responsible for the decrease in pulmonary compliance, increase in intrapulmonary shunting, and high mortality this syndrome carries.

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Influence of Hemorrhage on Adrenal Secretion, Blood Glucose and Serum Insulin in the Awake Pig

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A study was performed to quantitate the adrenal medullary and cortical response to hemorrhage in awake animals bled at different rates and to relate these responses to simultaneous changes in blood glucose and serum insulin. A series of awake pigs were bled either slowly or rapidly of 30% of their calculated blood volume. Infusions of exogenous epinephrine were performed in an additional series of unbled animals and infusions of epinephrine plus hydrocortisone were similarly performed in an additional series. Increase in blood glucose and epinephrine secretion rate following hemorrhage were found to be significantly dependent upon the rate of initial hemorrhage. Cortisol secretion was found to rise significantly during and following hemorrhage in both rapidly and slowly bled animals. Serum insulin levels remained at baseline levels during shock, despite the presence of significant hyperglycemia. In unbled animals infused with epinephrine at rates comparable to those measured in shock, elevations in blood glucose were markedly lower, shifting to the right of the dose-response curve during hemorrhage. Simultaneous infusions of cortisol and epinephrine resulted in a dose-response curve which did not differ significantly from that following infusion of epinephrine alone.

POSTHEMORRHAGIC HYPERGLYCEMIA was first described by Claude Bernard in 1877[5] and has since been well documented both in animal experiments and in clinical studies. Evidence has recently been presented that elevation of blood glucose is significantly related to the rate of initial blood loss, being much higher following rapid hemorrhage.[9] Although direct proof is lacking, the etiology of shock hyperglycemia has been attributed to an increased secretion of catecholamines during blood loss. The mechanism is thought to be principally the effect of epinephrine on hepatic glycogen breakdown as well as its more recently demonstrated suppressive effect on pancreatic insulin secretion.

The present study was performed to quantitate the adrenal medullary and cortical response to hemorrhage in awake animals bled at different rates and to relate these responses to simultaneous changes in blood glucose and serum insulin. A series of awake pigs were bled either slowly or rapidly of 30% of their calculated blood volume. The baseline adrenal epinephrine secretion rate (10.9 ± 1.6 ng/kg/min) obtained with the experimental model agreed closely with previously measured values. Changes in blood glucose correlated closely with epinephrine secretion rate ($r = 0.86$, $P < 0.001$), and both were higher in rapidly bled animals (80 ± 26 mg % vs 18 ± 13 mg %). The rate of adrenal corticosteroid secretion was increased more rapidly than epinephrine secretion during hemorrhage and its magnitude was not dependent on rate of initial hemorrhage.

In a second series of animals infused with epinephrine at rates similar to those found in shock, less hyperglycemia occurred, suggesting other contributing factors. Results were not altered by simultaneous infusion of hydrocortisone. No significant increase in insulin secretion occurred in response to hyperglycemia following blood loss. This is felt to represent suppression of insulin secretion by elevated levels of catecholamines.

Methods

Hemorrhage Study

All studies were performed upon young, unanesthetized, cross-bred pigs weighing 10 to 18 kg. All

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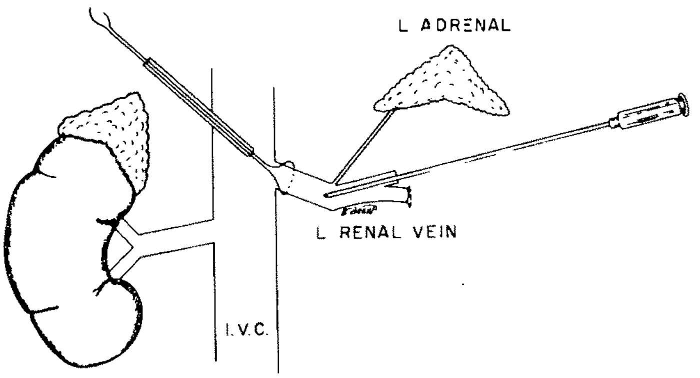

FIG. 1. Diagram of experimental preparation allowing intermittent determination of adrenal secretion rates.

animals were trained to tolerate suspension in a Pavlov stand without excitement. Twelve animals were anesthetized on the day prior to study and underwent a left nephrectomy with ligation of the left renal vein just distal to its orifice (Fig. 1). Although the right adrenal vein frequently was found to enter directly into the vena cava, the left adrenal vein was found to consistently enter into the left renal vein. A siliconized catheter was then placed in the renal vein stump and a silk choker was placed around the left renal vein at its junction with the inferior vena cava. Any tributaries of the renal vein other than the left adrenal vein were ligated and divided. The position of the choker and the catheter was carefully checked so that no obstruction to the adrenal vein was present when the choker was released. Additional catheters were placed in the inferior vena cava and aorta through the femoral vessels. The choker and all catheters were then brought through the skin of the back and taped in place. Allowed only water during the 10 hours preceding study, the pigs were fed after recovery from anesthesia.

On the day of the study, the experimental animal was placed in the Pavlov stand. After thirty minutes, baseline samples were obtained and the animals were then bled through the venous line of 30% of the calculated blood volume, either rapidly (30 min) or slowly (80 min). During each of three periods of 10% hemorrhage, the choker was tightened, allowing the entire left adrenal venous drainage to be collected and the time required to take the sample accurately recorded. Peripheral venous samples were drawn at the same time. Similar samples were drawn at 30, 60, and 90 minutes following the end of hemorrhage. Samples drawn after the initial hemorrhage accounted for an additional loss of 15% of the calculated blood volume.

In all animals vena cava glucose and insulin levels were measured during the sample periods. In 6 of the animals, adrenal epinephrine secretion rate and peripheral venous epinephrine and norepinephrine levels were also measured. In a second group of 6 pigs, adrenal corticosteroid secretion rates were determined. Autopsies were performed upon all animals and it was verified that catheter and choker position had not changed.

Blood volumes were calculated, employing a standard formula for pigs using T-1824[32], which has been checked frequently in our laboratory and has been found to be consistently accurate.

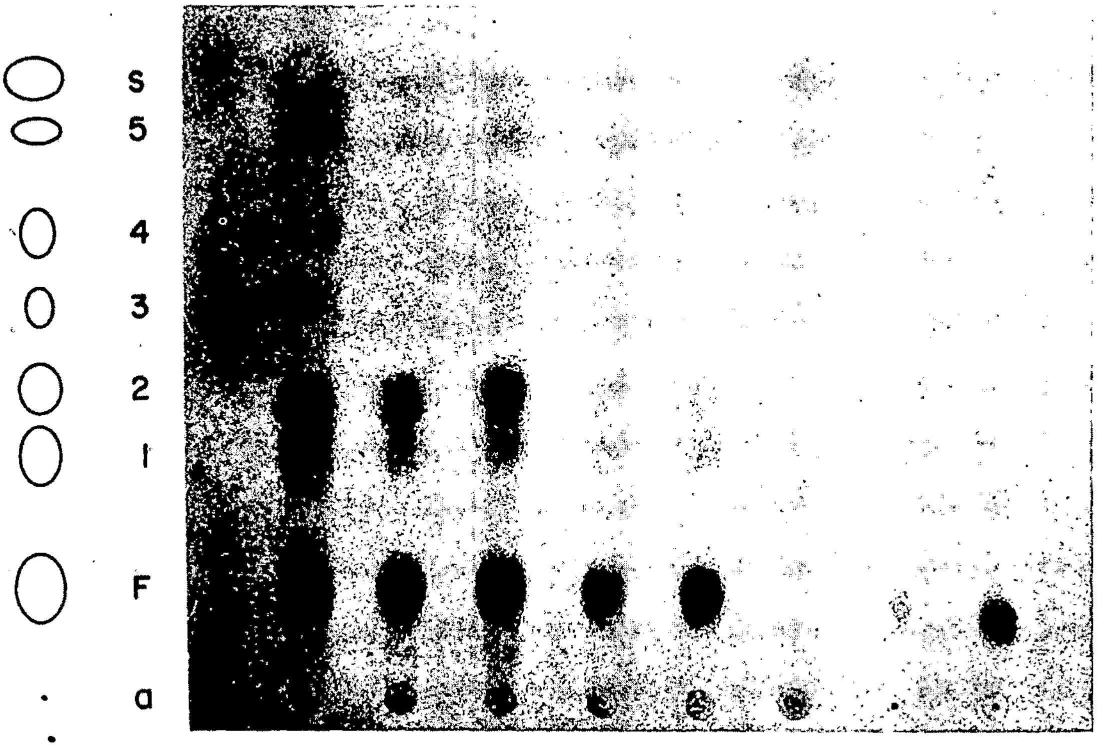

FIG. 2. A thin-layer chromatogram from one experiment. Reading from right to left the columns represent a 2 μg cortisol and 2 μg corticosterone standard; the pig adrenal venous plasma extract at the beginning of the experiment during initial 10% hemorrhage; and levels of the remaining extracts concluding with the 90-minute posthemorrhage extract on the far left. a = point of application, F = cortisol, 1 = corticosterone and cortisone, 2 = cortexolone (Reichstein's substance S), 3 = 11-B-hydroxyandrostenedione, 4 = cortexone (desoxycorticosterone) and 17-alpha-hydroxyprogesterone, 5 = progesterone, and S = unknown substance migrating with the solvent front.

Infusions in Unbled Animals

Infusions of exogenous epinephrine (8 to 1024 ng/kg/min) were performed in 12 animals which were awake and immobilized in a Pavlov stand. The epinephrine solution was infused through a catheter which had been placed in the inferior vena cava via a femoral cutdown on the day before the study. A Harvard Apparatus infusion pump was used for control of infusion rate, and oxidation of epinephrine was prevented by the addition of small amounts of ascorbic acid.

Infusions of epinephrine plus hydrocortisone (1 mg/kg/min) were similarly performed in an additional 12 animals.

Chemical Assays

Glucose determinations were performed using the O-toluidine reaction.[18] Insulin levels were measured using a standard immunoassay technique.[29] Plasma catecholamine concentrations were determined by a fluorometric method described elsewhere.[27] Intermittently, excitation and fluorescence spectra were checked, using a Farrand Mark I spectrophotofluorometer.

The total epinephrine secretion rate (TESR) was obtained by multiplying the left adrenal vein epinephrine concentration (microgram/L) by the left adrenal vein plasma flow (ml/min), dividing by the body weight (kg), and multiplying the last figure by 2, on the assumption that the right adrenal was secreting as much epinephrine as the left adrenal.

Adrenal vein plasma cortisol concentrations were determined by a method suggested by the work of Uetwiller and Keller.[30] Approximately 15 ml of plasma were placed in a 50 ml centrifuge tube which was filled with methane. After 15 seconds of shaking, the mixture was centrifuged at 1500 rpm for 5 minutes. (This step removed phenolic substances, especially estrogens.) The dichloromethane layer was aspirated and evaporated to dryness. The residue was spotted on a precoated silica-gel G plate impregnated with a 254 mμ phosphor; 10 μg and 2 μg standards of hydrocortisone were spotted on each plate. The plates were developed in 95:5 chloroform methanol for a distance of 13 to 15 cm, requiring about 60 to 90 minutes. The appearance of a typical thin-layer plate viewed under a 254 mμ hand lamp is shown in Fig. 2. The air-dried

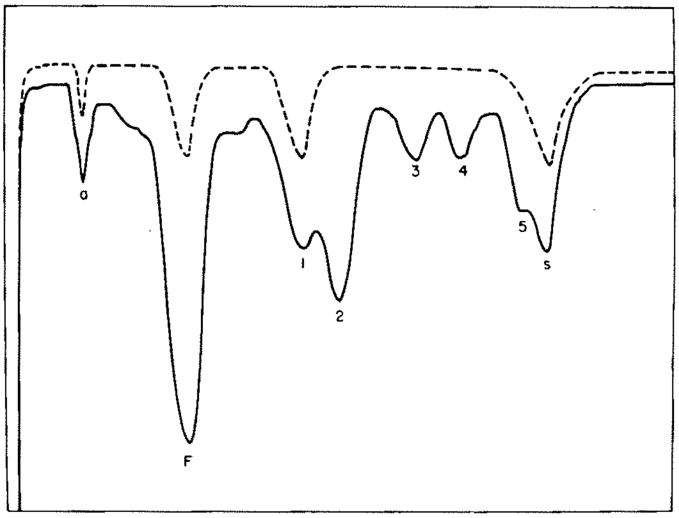

FIG. 3. Superimposed scans of two columns from a typical thin-layer plate. Abbreviations are the same as in Fig. 2. The top of the plate is on the right. The solid line is an adrenal plasma extract and the dotted line is from 2 μg cortisol and 1 μg corticosterone standards.

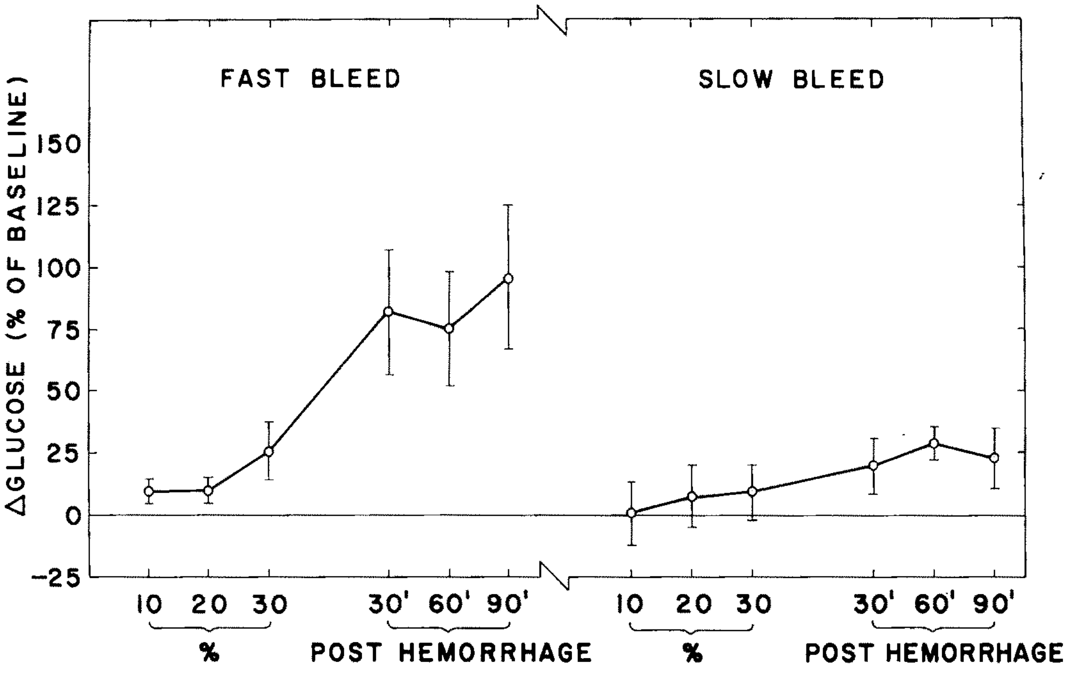

FIG. 4. Changes in blood glucose levels (± S.E.M.) during and following 30% hemorrhage in slowly and rapidly bled animals.

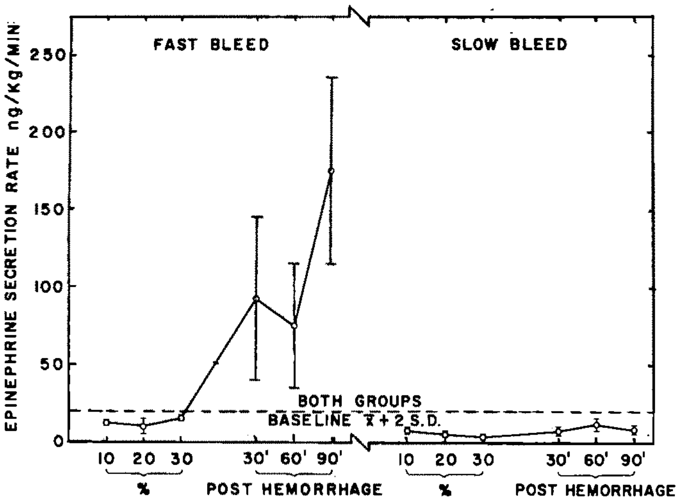

FIG. 5. Epinephrine secretion rates ($\bar{x} \pm 2$ S.D.) in rapidly bled and slowly bled animals during and following 30% hemorrhage.

plates were then placed in the thin-layer chromatogram scanning attachment of a Ferrand Mark I spectrophotofluorometer connected to a chart recorder. The excitation was set for 254 mμ with emission at 270 mμ. All slits were 5 mμ and the widest aperture was used. The quench profiles obtained from a sample and a standard are shown in Fig. 3.

The lower limit of detection of the method described was approximately 200 ng of cortisol with the instrument set to record at range 1. For less concentrated samples, the scale deflection could be increased 40 to 50% by setting the emission monochromator at 265 mμ and/or could be increased 3.3-fold by setting the range at 0.3.

The major glucocorticoid of pig adrenal venous plasma was found to be cortisol. Smaller quantities of cortexolone (Reichstein's substance S) were also identified. A third, faint spot represented the overlap between very small amounts of cortisone and corticosterone. All four of these substances were identified in extracts of pig adrenal. A fourth spot, also faint, represented the overlap between 17-α-OH-progesterone and cortexone (desoxycorticosterone). In preliminary studies it was found that the quenching intensity was always proportional to the logarithm of the weight. Accordingly, for each plate a curve of the two standards was plotted on semilog paper and the weight of cortisol in each dichloromethane extract was read from it. Although only cortisol was quantitated, it was apparent from inspection of the plates that whenever the concentration of cortisol increased, the concentrations of most of the other steroids also increased (Fig. 3). Cortisol concentrations were converted to total cortisol secretion rates by the same calculations described from TESR (vs).

Results

Hemorrhage Study

Increase in blood glucose following hemorrhage was found to be significantly dependent upon the rate of initial hemorrhage. Glucose values in rapidly bled animals had increased approximately 80 ± 26 (S.E.) mg% at 30 minutes posthemorrhage compared to an increase of 18 ± 13 mg% in the slowly bled group ($P = 0.05$) (Fig. 4). Similar significant differences were also found at the end of 60 and 90 minutes. Changes in blood pressure, expressed as per cent fall from baseline, were not significantly different between the rapidly and slowly bled animals.

Epinephrine secretion rate in the rapidly bled animals was not found to rise significantly during hemorrhage but was elevated at 30, 60, and 90 minutes following hemorrhage (Fig. 5). These rates are probably not miximal (see appendix). In contrast, no increase in the epinephrine secretion rate was demonstrated in slowly bled animals despite the loss of the same relative volumes of blood. The differences in epinephrine secretion response between the two groups is comparable to the previously described differences in blood glucose elevation.

Epinephrine secretion rates correlated closely with changes in blood glucose values ($r = .86$, $P < 0.001$). Venous epinephrine and norepinephrine levels correlated closely with adrenal secretion rates as would be expected ($r = .813$, $P < 0.001$) (Table 1). A more marked rise in peripheral norepinephrine levels was found in the rapidly bled animals. However, this experimental technique provided no direct measurement of the norepinephrine secretion rate, since in the pig, as in most animals, significant amounts of norepinephrine are secreted in extra-adrenal sites.

TABLE 1. *Mean Values (S.E.) of Peripheral Venous Epinephrine and Norepinephrine (ng/ml) During and Following Hemmorrhage*

	10%	20%	30%	10 min	20 min	30 min
Rapidly Bled						
Epinephrine	0.41 ± .26	2.45 ± .48	10.18 ± 4.74	8.50 ± 5.18	13.12 ± 6.46	26.76 ± 16.27
Norepinephrine	0.26 ± .14	0.28 ± .13	1.50 ± .44	1.65 ± .32	1.55 ± .32	24.91 ± 13.15
Slowly Bled						
Epinephrine	0.62 ± .07	0.77 ± .16	0.95 ± .45	2.98 ± .31	0.52 ± .30	0.07 ± .02
Norepinephrine	0.41 ± .25	0.08 ± .02	0.05	0.05	1.08 ± .11	0.67 ± .04

Cortisol secretion was found to rise significantly during and following the end of hemorrhage in both rapidly and slowly bled animals (Fig. 6).

No increase in serum insulin levels occurred in response to the hyperglycemia following blood loss (Fig. 7). Serum insulin levels remained at baseline levels (33.8 ± 8.0 $\mu\mu$/ml) during shock, despite the presence of significant hyperglycemia.

Infusion Study

When unbled animals were infused with epinephrine at varying dose levels and the subsequent changes in blood glucose were graphed, a typical dose-response curve was obtained (Fig. 8). The curve, however, was shifted significantly to the right of that obtained during the hemorrhage study, and it was suspected that increased levels of glucocorticoids following hemorrhage might add to the hyperglycemic effect of epinephrine. For this reason, simultaneous infusions of cortisol and epinephrine were performed in an additional series of 12 animals to determine the effect of high infusion rates of cortisol on the epineprhine-glucose dose-response curve. The dose-response curve so obtained, however, did not differ significantly from that following infusion of epinephrine alone.

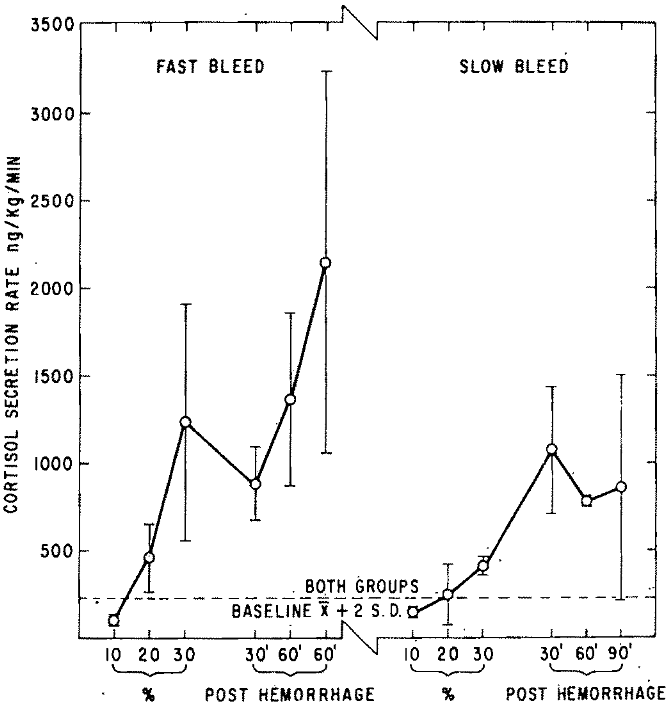

FIG. 6. Cortisol secretion rates (x̄ ± 2 S.D.) in rapidly bled and slowly bled animals during and following 30% hemorrhage.

Discussion

Baseline Secretion Rate

The experimental model described appears to furnish a valid and relatively simple method of studying adrenal response in an awake animal, yielding results similar to previously reported methods. The baseline adrenal epinephrine secretion rate was calculated as 10.9 + 1.6 ng/kg/min. Relatively little variation in the baseline values was found and this is felt to be due to the relatively long sampling period of 10 minutes. Similar baseline values in experimental animals have been reported: Walker et al. measured mean secretion rates of 11.1 and 5.9 ng/kg/min in two groups of unanesthetized dogs,[33] and Ikeda reported a basal adrenal epinephrine secretion rate varying from 4 to 11 ng/kg/min during two consecutive control periods in dogs.[19] The baseline secretion rate was also similar to that predicted in man to be 8 ng/kg/min by Vendsalu[31] and 10 ng/kg/min by Cohen et al.[11] more recently. A directly measured value in man of 8.7 ng/kg/min has been obtained by Sapira and Bron,[26] using a direct adrenal vein catheterization technique.

Epinephrine Secretion Rate

Blood Glucose Levels. Increase in blood glucose levels was found to be significantly dependent upon the rate of initial hemorrhage. This agrees with the previous report of Carey and Wallack in which a similar relationship between rate of hemorrhage and hyperglycemic response was found in anesthetized pigs.[9] Increase in epinephrine secretion rate was found to be similarly dependent upon initial rate of hemorrhage. It is significant that slowly bled animals developed only a minimal rise in epinephrine secretion rate despite the loss of approximately 42% of calculated blood volume. Fall in blood pressure was not significantly different between the two groups. This suggests that the stimulus for epinephrine secretion is dependent on rate of decrease of volume. Recently it has been recognized that the rate of plasma refill is considerably more rapid than previously believed.[8] Although this could not be calculated from data obtained in the present study, it is possible that plasma refill may have occurred rapidly enough in the slowly bled animals that the stimulus for epinephrine secretion was minimal. In a study of hemorrhagic shock performed later in this laboratory on awake pigs bled rapidly of 45% of calculated blood volume, plasma refill calculated from chages in hematocrit following hemorrhage was estimated to restore 25% of original bled volume within one hour. An additional explanation is suggested by a recent clinical study of variation in hemodynamic responses following hemorrhage over a relatively long (>4 hrs) or short (<4 hrs) period.[2] Higher cardiac outputs, arterial pressures, and central blood volumes were found in patients who had bled slowly. This was felt to represent the effects of a

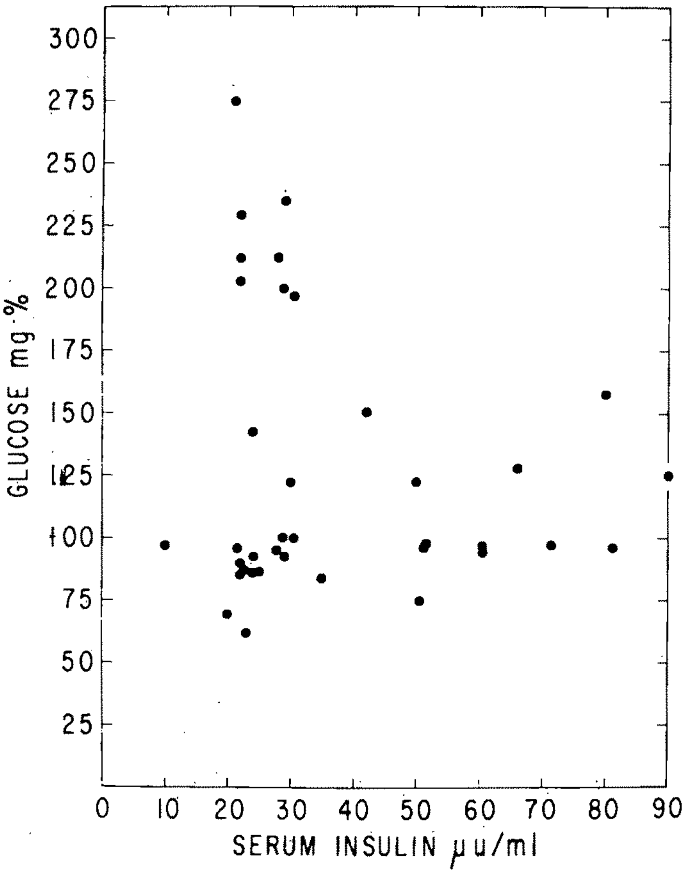

FIG. 7. Blood glucose (mg%) versus serum insulin (μu/ml) determined during and following 30% hemorrhage.

redistribution of blood volume into the central pool of blood.

The adrenal epinephrine secretion rate correlated closely with blood glucose levels following hemorrhage. If epinephrine secretion was primarily responsible for hyperglycemia, as was suspected, it was felt that similar levels of hyperglycemia would be achieved by infusion of epinephrine at similar rates into nonbled animals. When nonbled animals were infused with epinephrine at rates comparable to those measured in shock, elevations in blood glucose were markedly lower, shifting to the right, the dose-response curve during hemorrhage (Fig. 8). The presence of the adrenal medulla has been previously shown to be necessary for the occurrence of the hyperglycemic response.[14,23] The present data, however, indicate that additional humoral factors or peripheral metabolic changes significantly alter or contribute to the effect of epinephrine on carbohydrate metabolism during hemorrhagic shock.

Cortisol Secretion

Steroids are known to modify the kinetics of catechol-sensitive reactions.[1] It is also well established that adrenal cortisol secretion increases following hemorrhage, although the exact mechanism triggering this release is incompletely understood. Because of the possible contributions of elevated cortisol to hyperglycemia following hemorrhage, adrenal cortisol secretion was found to increase in response to hemorrhage. The adrenal cortical response was found, however, to differ from the medullary response in several important respects.

A marked difference was found between the rapidity with which the adrenal medulla and the cortex responded to the stimulus of hemorrhage. In most animals a significant increase in cortisol secretion was found during the second 10-minute period of hemorrhage (while blood loss was approaching 20% of blood volume). This response differed from that of adrenal epinephrine secretion, which was only first significantly increased in samples taken 30 minutes following hemorrhage. Although the chemical methods used did not allow simultaneous measurement of both epinephrine and cortisol in the same animals, results indicate that cortisol secretion occurs much more rapidly than epinephrine secretion in response to hemorrhage. This is in agreement with studies reported by Gann and Egdahl who found that adrenal vein levels of 17-OH corticosteroids in dogs were elevated in samples drawn 15 minutes following hemorrhage.[18]

No relationship was found between cortisol secretion and rate of hemorrhage. Even in slowly bled animals, cortisol secretion was elevated before hypotension occurred. These results agree with previous studies

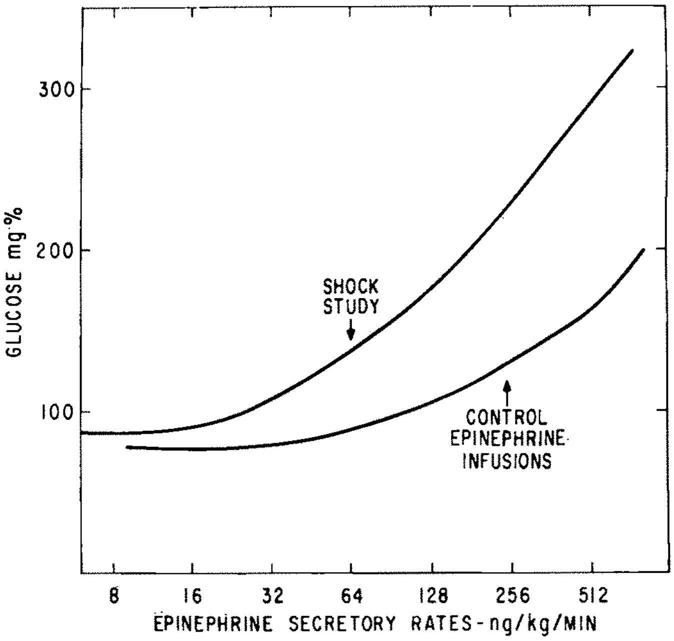

FIG. 8. Glucose-epinephrine response curves determined during adrenal secretion response to hemorrhage and during control epinephrine infusions.

demonstrating that the stimulus for adrenal cortical secretion is not dependent upon hypotension alone.[1,15]

Lack of correlation between glucose and cortisol secretion, although a significant part of the physiologic response to hemorrhage, seems to indicate that increased cortisol secretion does not significantly contribute toward hyperglycemia following hemorrhage. It was in order to verify this that unbled animals were "infused" with both epinephrine and cortisol. The glucose-epinephrine dose-response curve obtained by infusion of unbled animals with epinephrine alone was not significantly shifted by the additional infusion of cortisol.

Assuming, for the above reasons, that elevated levels of cortisol do not significantly alter or increase effects of epinephrine during shock, additional hyperglycemic factors following hemorrhage are poorly defined. Growth hormone is known to increase following injury and blood loss.[28] This was previously felt to be a somewhat delayed reaction; however, in a study of Vietnam War casualties, levels of both glucose and GH were elevated on admission to the hospital.[6] But the relationship between growth hormone and hyperglycemia is poorly defined. In the pig, growth hormone has been shown to cause a minimal rise in blood glucose[15] and it is doubtful that this alone would account for the unexplained hyperglycemia.

Peripheral glucose utilization is an additional factor which must be considered. The decreased cellular perfusion associated with hemorrhage and shock causes a shift of cellular metabolism from aerobic to anaerobic. Because of this, and because of epinephrine's effect of suppressing insulin secretion, it is likely that glucose utilization is decreased. Peripheral glucose changes during hemorrhage have been extremely difficult to quantitate in vivo and at the present time these are incompletely understood. However, if glucose utilization is decreased during hemorrhagic shock, this would offer a possible mechanism to account for the hyperglycemia noted in this study.

Insulin Secretion

With the availability of accurate insulin immunoassay techniques, investigation of change in insulin secretion during various shock states has begun. Comparison between different experimental shock studies in this area is difficult however, because of varying responses in different animal species as well as significantly different shock preparations. A rise in both insulin secretion and plasma insulin levels has been demonstrated in dogs. However, some evidence was found for a partial inhibition of insulin release when intravenous glucose tolerance tests were performed on dogs in hemorrhagic shock.[23] Recent studied in subhuman primates have failed to demonstrate rises in serum insulin in response to hemorrhage.[10,12] In fact, during the first hour in a hypotensive state, insulin values fell significantly below control levels, returning during the second hour to control levels. In addition, decreased response to tolbutamide was demonstrated following hemorrhage. Failure of insulin response to hyperglycemia has been reported in man during hypothermia,[4] cardiogenic shock,[13] and hemorrhagic shock.[7,20] In the latter study, insulin values were found to rise in response to hyperglycemia following initiation of resuscitative measures. The high levels of epinephrine found in shock are felt to be the predominant factor contributing to the observed failure of plasma insulin rise. This inhibitory effect of epinephrine has been demonstrated in humans,[25] in pigs,[17] and in isolated pancreatic slices, and appears to be predominantly an alpha receptor effect.[24] In the present study no evidence for increased insulin response to hyperglycemia was found. This suggests significant suppression of insulin secretion, as plasma insulin levels have been previously demonstrated to increase in pigs (although relatively less than in man) in response to hyperglycemia.[21] Findings were consistent with epinephrine effect, as hyperglycemia was almost always associated with elevated epinephrine secretion rates. Mean values of insulin decreased slightly during the study but this was not statistically significant. Changes in pancreatic blood flow and peripheral insulin breakdown are also of significance but are poorly understood at present.

Appendix

A 15-kg pig with a left adrenal weighing 1.671 gm containing 140 μg of epinephrine per gm has total body stores of epinephrine of approximately 470 μg. At 15-kg pig at a basal total epinephrine secretion rate of 10 ng/kg min would require only 9 μg of epinephrine during an hour. With the epinephrine secretion rate at 100 ng/kg/min for 100 minutes, only 150 μg would be required, or less than a third of the available. None of our animals reached or maintained a 300 ng/kg/min total epinephrine secretion rate for 100 minutes, which would have required 450 μg of epinephrine, i.e. over 95% of that available.

If the elevated total epinephrine secretion rate of 100 ng/kg/min were maintained for 300 minutes, 450 μg of epinephrine would be required. However, this would not be greater than 95% of the total available for the following reason: At a basal secretion rate of 10 ng/kg/min a 15-kg pig would have to synthesize 150 ng/min to maintain steady states. With a total body store of 470 μg this would mean that 03% of the total body store is synthesized per minute, or 9.6% of the original total body store would have been newly synthesized during the 300 minutes.

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The Relationship Between Muscle Surface pH and Oxygen Transport

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The relationship between muscle surface pH (pH_M) and the arterial-venous oxygen content difference (AVO_2D) was studied in 4 patients undergoing reconstructive arterial surgery and in 6 patients undergoing acute normovolemic hemodilution. There was a consistent inverse relation between pH_M in the ischemic lower extremity and the femoral AVO_2D before, during and after aortic clamping. There was also an inverse relation between AVO_2D and pH_M during hemodilution. These data confirm that pH_m is a reliable indicator of tissue perfusion and correlates with the AVO_2D.

SYSTEMIC OXYGEN TRANSPORT (SO_2T) is defined as the product of the cardiac output (CO) and the arterial oxygen content. When oxygen transport is reduced due to a reduction in flow or a decrease in arterial oxygen content such as that caused by a reduced oxygen carrying capacity (O_2CC) one of the compensatory mechanisms may be an increase in the extraction of oxygen from the blood perfusing the tissues, that is, an increase in arterial-venous oxygen content difference (AVO_2D). The relationship between the increase in the AVO_2D and the adequacy of oxygen supply to the tissues is uncertain. Muscle surface pH (pH_M) has been shown by Couch et al.[1] to be a reliable index of tissue perfusion in various clinical situations, a finding confirmed by Gazzaniga[3] and Filler.[2]

In the present study, the relationship between the AVO_2D and pH_M was evaluated in the ischemic extremity during reconstructive vascular surgery and during acute normovolemic hemodilution (HD).

Materials and Methods

Two groups of patients were studied. Group I consisted of four men, ages 35 to 58 years, undergoing reconstructive arterial surgery of the lower extremities. Patient 1 underwent a right external iliac endarterectomy. Patients 2, 3 and 4 underwent bilateral aortofemoral reconstruction. Patient 4 had intraoperative prebleeding with hemodilution prior to the vascular procedure. A right-angle Ingold pH probe* and Corning pH meter were employed to monitor muscle surface pH.[1] The muscle surface pH probe was placed on the vastus lateralis muscle of the more ischemic lower extremity and a second pH probe was placed on the biceps muscle of the uninvolved upper extremity. A radial artery line was placed percutaneously and used for pressure monitoring and the measurement of arterial gases and pH. A central venous line was placed in the external jugular vein and placed either in the right atrium or in the pulmonary artery. A cannula was inserted into the common femoral vein via one of its branches at the time of exposure of the femoral artery. Large vessel hematocrit (LVH) was measured in triplicate by centrifugation of heparinized blood samples in Wintrobe tubes at 3,000 rpm for 5 minutes. Arterial, central venous and femoral vein blood gases and pH were measured with a Radiometer Acid Base Analyzer (Copenhagen PHM 1971). Oxygen saturation was measured by an Instrumentation Laboratory Cooximeter (Model 182). Arterial and femoral vein lactate and pyruvate levels were also measured by methods described by Gloster[4] and Hohorst.[5] The pH_M of the involved lower extremity and the upper extremity were recorded. Measurements were taken prior to cross clamping of the aorta, during the cross clamp period, and after release of the cross clamp at intervals. In the patient undergoing hemodilution, measurements were taken before and after HD and before, during and after cross clamping.

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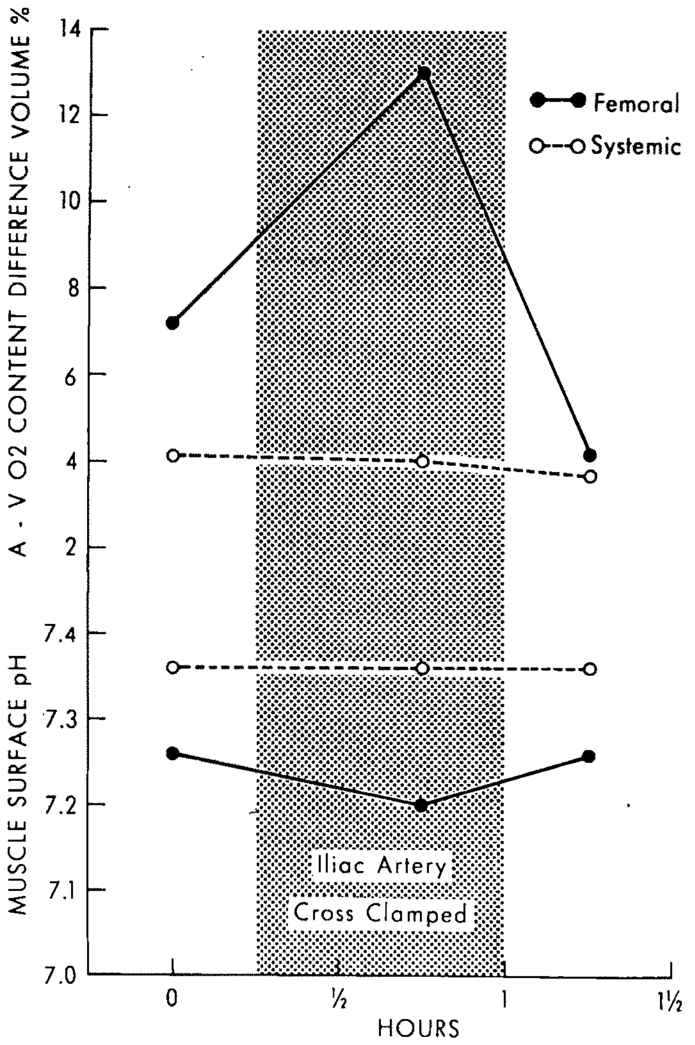

FIG. 1. Study of Subject 1 during right external iliac endarterectomy. Femoral and systemic A–V O_2 content difference and muscle surface pH in ischemic extremity (solid line) and in upper extremity (dotted line), before, during and after iliac artery clamping.

Group II. In this group the relationship between systemic AVO_2D and pH_M in the upper extremity was correlated during HD. It included 6 patients from 25 to 51 years of age who were undergoing total hip replacement. In 4, HD was conducted in two stages using Plasmanate† and lactated Ringer's solution as the hemodiluting agent in a volume twice that of the shed blood. In two, lactated Ringer's solution alone was used in a volume three times that of the shed blood. Hemodilution was conducted over 20 minutes with arterial and venous bleeding, and simultaneous infusion of the hemodiluting agent. At the end of the operation, the patient's blood was reinfused. Blood vessel cannulation consisted of a radial artery line, and a four channel thermodilution Swan-Ganz catheter[5] directed into the pulmonary artery via an antecubital venous cutdown. CO was measured by the thermodilution technique.[6] The average of 5 readings was used. The muscle surface pH probe was placed on the biceps muscle. LVH was measured as described above. Arterial and central venous blood P_{O_2} and P_{CO_2}, pH, oxygen saturation and lactate and pyruvate concentration were measured. In the 4 patients undergoing two stage HD, measurements were taken at baseline and twenty minutes after each stage. In the two patients receiving lactated Ringer's solution measurements were taken before and 20 minutes after HD.

Results

Group I. As indicated in Figures 1, 2, 3, 4 and Table I there was an inverse relationship between the pH_M in

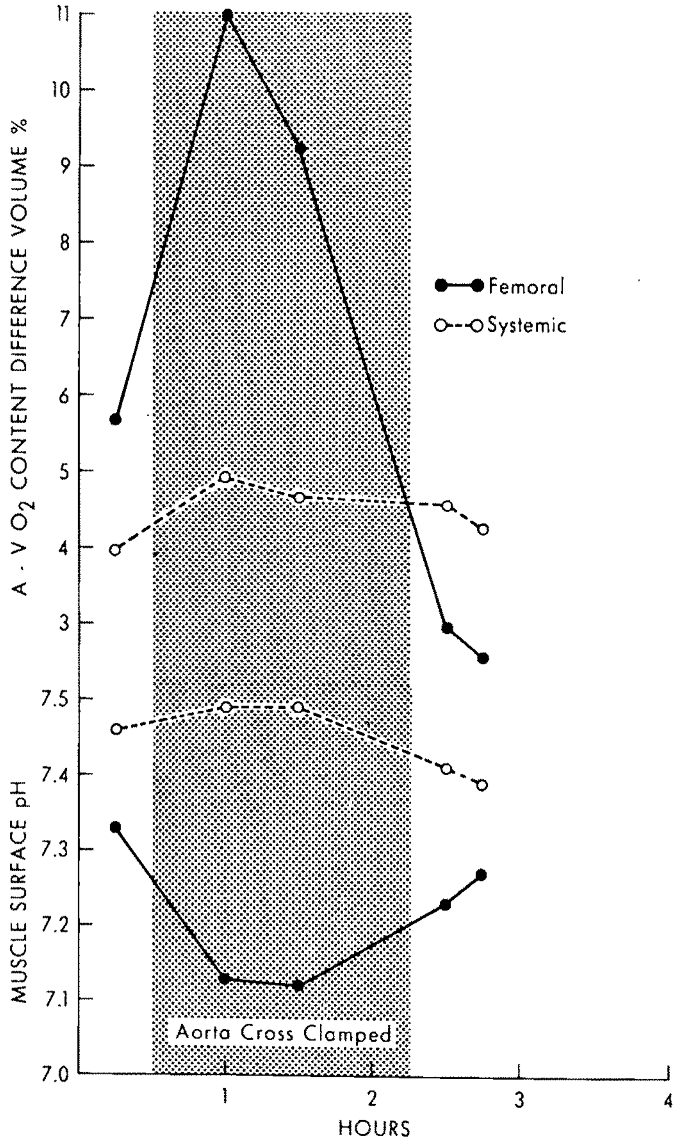

FIG. 2. Femoral and systemic A–V O_2 content difference and muscle surface pH, before, during and after aortic cross clamping in Subject 2, undergoing aorto femoral bypass graft.

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† Plasmanate (Cutter) contains 5% protein, mainly albumin, in 0.15 M concentrated saline.

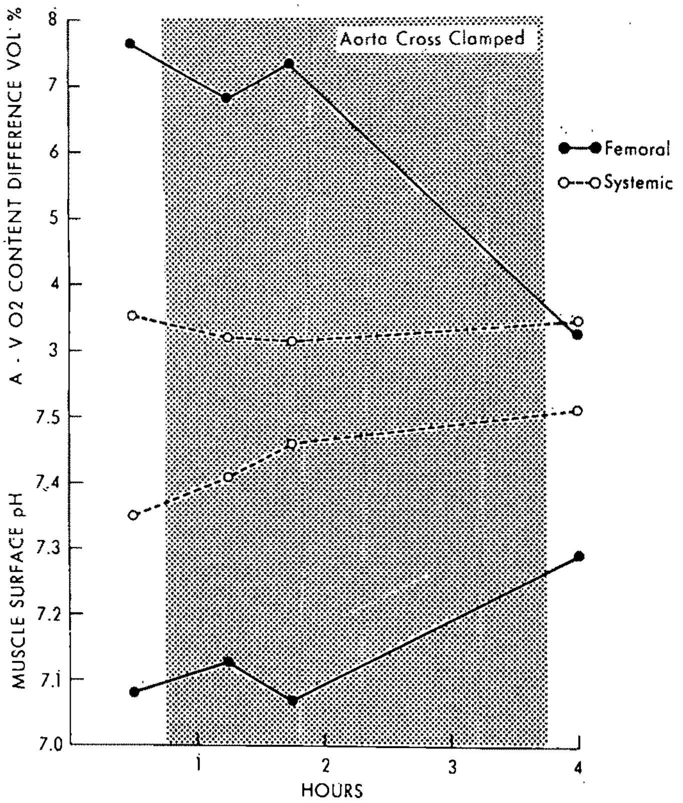

FIG. 3. Subject 3. A–V O_2 content difference and muscle surface pH during aortic cross clamping for aorto femoral bypass grafting.

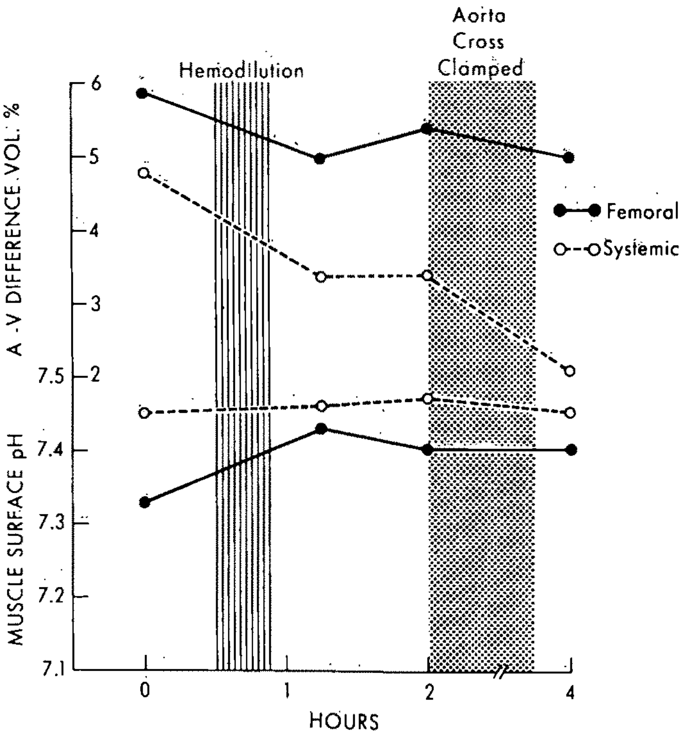

FIG. 4. Systemic and femoral A–V O_2 content difference and muscle surface pH in Subject 4 with hemodilution and aortic clamping during aorto femoral bypass graft.

the ischemic extremity and the femoral AVO_2D. The two graphs are mirror images of each other. In all cases, after aortic clamping the AVO_2D rose and pH_M fell while after removal of the clamp these measurements moved in opposite directions. It is notable that these changes occurred in variable degrees. Subject 4 underwent hemodilution prior to cross clamping for an aorto-iliac reconstruction. With HD the AVO_2D in the ischemic leg fell from 5.85 to 4.95 vol% and the pH_M remained stable (7.40–7.43) at 30 and 60 minutes of cross clamping, and after release of the cross clamp. Prior to cross clamping, the AVO_2D was 4.95 vol%. It rose slightly to 5.33 vol% after 30 minutes of cross clamping and fell to 4.95 vol% 15 minutes after release of the clamp, with a stability similar to that of pH_M. Figs. 1–4 also depict the changes in the systemic AVO_2D and the pH_M in the involved upper extremity. As is shown in these figures and in Table 1, the pH_M is always higher in the normal upper extremity than in the ischemic lower extremity and has

TABLE 1. *Relationship Between Muscle Surface pH and A-V O_2 Content Difference*

	Muscle Surface pH in Ischemic Lower Extremity						Femoral A-V O_2 Content Difference		
	Before CC	30′ CC	60′ CC	15′ R	30′ R	60′ R	Before CC	30′ CC	15′ R
1	7.26	7.20	—	7.26	7.26	7.28	7.17	13.02	4.17
2	7.33	7.13	7.12	7.23	7.26	7.27	5.6	13.98	3
3	7.08	7.13	7.07	7.19	7.24	7.29	7.65	6.85	3.25
4	7.43	7.40	7.43	7.40	7.39	—	4.95	5.33	4.95
Mean	7.275	7.215	7.207	7.27	7.288	7.280	6.343	9.745	3.843
SEM±	0.074	0.064	0.113	0.046	0.034	0.006	0.638	2.170	0.447
	Muscle Surface pH in Non-Ischemic Upper Extremity						Systemic A-V O_2 Content Difference		
1	7.36	7.36	—	7.36	7.36	7.36	4.16	4.03	3.72
2	7.46	7.49	7.49	7.41	7.41	7.39	3.99	4.97	4.59
3	7.35	7.41	7.46	7.57	7.48	7.51	3.53	3.2	3.45
4	7.43	7.47	7.47	7.45	7.45	—	3.35	3.36	2.06
Mean	7.40	7.433	7.473	7.448	7.425	7.42	3.758	3.140	3.455
SEM±	0.027	0.030	0.009	0.045	0.026	0.046	0.190	0.809	0.525

TABLE 2. *Changes in Arterial (A) and Femoral Vein (FV) Lactate and Pyruvate in Ischemic Extremity*

	Before CC			30′ CC			60′ CC			15′ R		
	L	P	L/P	L	P	L/P	L	P	L/P	L	P	L/P
1 A	0.9	0.07	12.85	1.1	0.09	12.22	—	—	—	1.4	0.12	11.66
FV	1.4	0.08	17.5	1.4	0.12	11.66	—	—	—	1.7	0.12	14.16
2 A	1.2	0.07	17.14	1.7	0.10	17	1.5	0.08	18.75	1.9	0.14	13.57
FV	1.3	0.08	16.25	1.7	0.12	14.16	1.7	0.12	14.16	2.0	0.15	13.33
3 A	2.2	0.23	9.56	2.1	0.17	12.35	1.5	0.12	12.5	1.5	0.09	16.66
FV	2.4	0.21	11.42	2.7	0.19	14.21	2.2	0.16	13.75	2.2	0.11	20.0
4 A	1.8	0.15	12	1.9	0.15	12.66	—	—	—	1.9	0.13	14.61
FV	1.7	0.12	14.6	2.0	0.15	13.33	—	—	—	2.5	0.15	16.66
Mean												
A	1.525	0.130	12.888	1.700	0.128	13.588	1.60	0.100	15.625	1.675	0.120	14.125
FV	1.70	0.123	14.943	1.950	0.145	13.34	1.95	0.140	13.955	2.10	0.133	16.038

about the same degree of stability as the AVO_2D in the same extremity. As shown in Table 2, there was not a close correlation between pH_M and the changes in arterial and femoral venous blood and pyruvate concentrations, and lactate/pyruvate ratios. The arterial and femoral venous blood pH, as shown in Table 3, moved slightly in the same direction as pH_m. The changes in mean blood pressure and hematocrit are shown in Table 4.

Group II. In this group of patients the correlation between pH_M and the AVO_2D is shown in Table 5. In the four patients undergoing two stage Plasmanate HD, it was found that SO_2T was reduced only slightly despite the great decrease in oxygen carrying capacity (O_2CC). Thus after HD_1 the SO_2T was 88% of the control value and after HD_2, 83%. Concurrently the O_2CC was reduced to 70% and 54.5%. The pH_M at each stage of HD rose slightly and this was associated with a concurrent decrease in the systemic AVO_2D (Fig. 5 and Table 5). In Subject 4 of Group I, who underwent one stage HD with Plasmanate prior to the reconstructive arterial surgery, SO_2T was increased due to a marked rise in CO. The systemic AVO_2D fell from 4.8 to 3.35 vol % while pH_M rose slightly from 7.40 to 7.43 (Fig. 4). In the two patients with lactated Ringer's solution HD in whom SO_2T fell, the AVO_2D rose and pH_M fell (Fig. 6). The correlation between pH_M and arterial and central venous blood pH was not close (Table 6), but as indicated in Table 7 there was close correlation between pH_M and CO and an inverse relationship of pH_M with SO_2T.

TABLE 3. *Changes in Arterial and Femoral Venous pH*

	Arterial pH			Femoral Venous pH		
	Before CC	30′ CC	15′ R	Before CC	30′ CC	15′ R
1	7.440	7.441	7.430	7.385	7.375	7.393
2	7.420	7.395	7.445	7.361	7.331	7.381
3	7.500	7.471	7.437	7.385	7.367	7.381
4	7.498	7.505	7.465	7.443	7.469	7.401
Mean	7.465	7.453	7.444	7.394	7.386	7.389
SEM ±	0.020	0.023	0.008	0.017	0.029	0.005

Discussion

In this study pH_M was measured in correlation with tissue perfusion and AVO_2D. In the patients with peripheral arterial occlusive disease, blood flow could not be measured, because measurement of femoral artery blood flow would not include flow through collaterals. This study did show an inverse relationship between the AVO_2D measured across the ischemic extremity and pH_M during the cross clamping of the aorta and after perfusion, but the degree of change for both factors was variable probably because of variable flow in the collateral arteries. This relationship is demonstrated in Fig. 6 and the correlation coefficient was −.7061 ($P < 0.05$). The best fit straight line calculated from the linear regression equation is shown in Fig. 7. In Subject 3, application of the cross clamp resulted in a slight rise of pH_M and a slight fall in AVO_2D initially. This seemingly paradoxical change was almost certainly related to other factors such as alterations in blood pressure and to the abundance of collateral flow. Nevertheless in this patient the inverse relationship between the AVO_2D and the pH_M was consistent and as the period of cross clamping continued, pH_M fell and the AVO_2D rose. Following reperfusion, there was a marked fall in the AVO_2D and a marked rise of pH_M.

The maintenance of SO_2T during HD is dependent upon an increase in blood flow. This is probably due to a reduction of blood viscosity. It is not known whether

TABLE 4. *Changes in Mean Blood Pressure during Vascular Reconstruction*

	Mean Blood Pressure mm Hg			Mean Hematocrit %		
	Before CC	30′ CC	15′ R	Before CC	30′ CC	15′ R
1	125	100	100	46.0	46.6	44.7
2	95	82	95	46.0	40.7	45.1
3	90	95	110	42.7	40.2	43
4	95	90	95	27.2	25.8	34.3
Mean	101.25	91.75	100	40.40	38.33	41.75

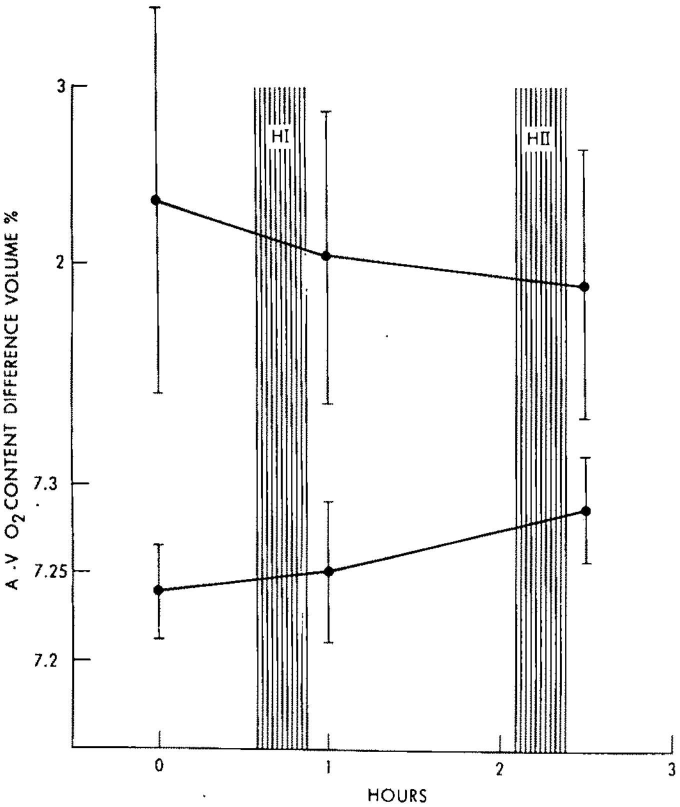

FIG. 5. Change in A–V O_2 content difference and muscle surface pH during two stage hemodilution (H_1 and H_2) with Plasmanate. Mean of Subjects 5, 6, 7 and 8 with SEM shown.

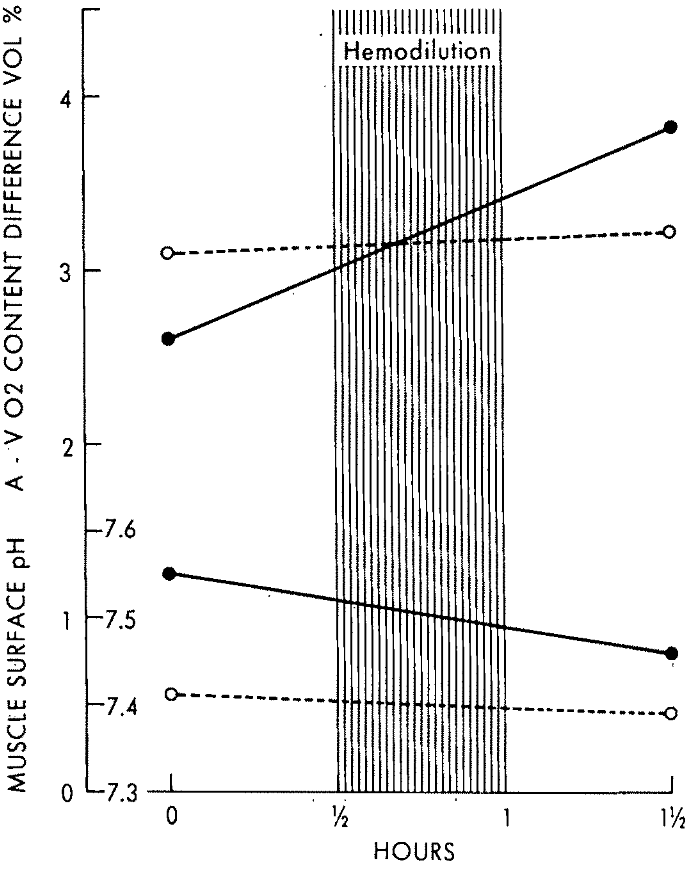

FIG. 6. A–V O_2 content difference and muscle surface pH in Subjects 9 (solid line) and 10 (dotted line) during one stage hemodilution with lactated Ringer's solution.

this compensatory increase in flow can occur in the presence of occlusive vascular disease. For this reason, the patient undergoing intraoperative prebleeding with HD prior to aorto-iliac reconstruction was most interesting. Hemodilution resulted in a decrease in the AVO_2D across the ischemic extremity while pH_M rose, suggesting improved tissue perfusion and oxygenation despite the reduction in O_2CC. This would only be possible if flow was increased. Thus the decrease in viscosity and resultant increased flow compensated for the reduced O_2CC despite the occlusive vascular disease.

TABLE 5. *Changes in A-V O_2 Content Difference and Muscle Surface pH in Hemodilution*

	Two Stage Plasmanate Hemodilution					
	A-V O_2 Content Difference			Muscle Surface pH		
	Baseline	HD_1	HD_2	Baseline	HD_1	HD_2
5	0.63	0.62	0.66	7.325	7.265	7.285
6	1.53	1.57	1.56	7.226	7.270	7.335
7	5.56	4.30	4.12	7.230	7.320	7.320
8	1.67	1.65	1.25	7.190	7.130	7.200
Mean	2.35	2.03	1.90	7.24	7.25	7.29
SEM ±	1.09	0.79	0.76	0.03	0.04	0.03
%	100	94.3	88.9	100	102.4	120.4
	One Stage Lactated Ringer's Hemodilution					
9	2.46		3.83	7.55		7.46
10	3.10		3.18	7.41		7.39
Mean	2.78		3.51	7.48		7.425
%	100		126.3	100		99.3

TABLE 6. *Changes in Arterial and Venous pH in Hemodilution*

	Two Stage Plasmanate Hemodilution					
	Arterial pH			Venous pH		
	Baseline	HD_1	HD_2	Baseline	HD_1	HD_2
5	7.410	7.440	7.438	7.410	7.400	7.402
6	7.380	7.370	7.390	7.350	7.350	7.360
7	7.440	7.453	7.480	7.430	7.428	7.426
8	7.330	7.340	7.342	7.318	7.315	7.322
Mean	7.390	7.401	7.413	7.377	7.373	7.376
SEM ±	0.023	0.027	0.030	0.026	0.025	0.023
	One Stage Lactated Ringer's Hemodilution					
9	7.38		7.38	7.36		7.37
10	7.36		7.37	7.34		7.36
Mean	7.37		7.375	7.35		7.365

TABLE 7. *Changes in Cardiac Output and SO_2T in Hemodilution*

	Two Stage Plasmanate Hemodilution					
	Cardiac Output ml/min			Systemic Oxygen Transport ml/min		
	Baseline	HD_1	HD_2	Baseline	HD_1	HD_2
5	2714	3744	4302	264	466	446
6	5008	5822	7200	992	859	794
7	3207	4121	3334	659	559	495
8	5209	5800	7184	913	740	733
Mean	4034	4871	5505	756	656	617
SEM ±	629	547	993	121	88	85
%	100	120.7	136.5	100	86.7	81.6
	One Stage Lactated Ringer's Hemodilution					
9	4400		4600	356		275
10	4600		5100	464		351
Mean	4500		4850	410		313
%	100		107	100		76

The arterial and femoral venous blood lactate and pyruvate concentrations (Table 2) were not substantially changed during the cross clamping period, probably because the areas of reduced arterial perfusion which were producing increased amounts of lactic acid due to anaerobic glycolysis were also returning very little blood to the venous circulation. At 15 minutes after reflow, however, both arterial and venous lactate concentrations were increased by 25 to 50% in Subjects 1 and 2. In patient 3, who had relatively little change of pH_M and AVO_2D during cross clamping (suggestive of abundant collateral flow), the increase of blood lactate was predictably small during reflow. A similar finding occurred in Subject 4 where hemodilution may have been responsible for minimizing ischemia and changes of pH_M and AVO_2D during cross clamping.

The lack of change in blood pH in the presence of major changes in pH_M in the ischemic extremity has been previously observed, and is attributable to the efficiency and abundance of the blood buffering systems.

The hemodynamic data in the four patients undergoing two stage HD have been previously reported by us[7] (Table 7). CO was increased after each stage of HD with a decrease in the AVO_2D and an increase in the pH_M. This was also found in Subject 4 of Group I in whom HD was carried out prior to the reconstructive surgery. However, in the HD conducted with lactated Ringer's solution, in agreement with the findings in other patients,[8] CO was only mildly increased (Table resulting in a decrease in the SO_2T. The AVO_2D rose as oxygen extraction increased and pH_M fell.

This study suggests that a rise in the AVO_2D is associated with the fall in pH_M probably because of reduced tissue perfusion, oxygen deprivation, and compensatory anaerobic glycolysis.

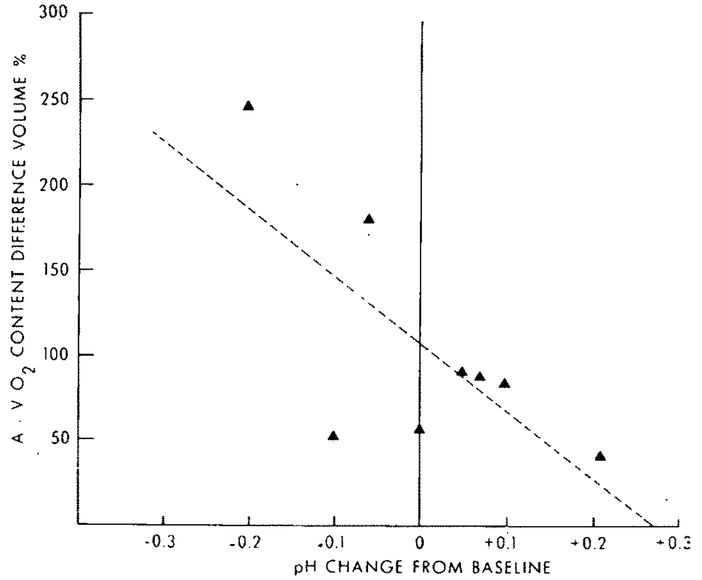

FIG. 7. Relationship between A–V O_2 content difference expressed as percentage of baseline value, and the change in muscle surface pH from the baseline value. Dotted line is the best fit straight line calculated from the linear regression equation.

Acknowledgments

The authors wish to express their gratitude to Dr. F. D. Moore for advice and encouragement, and to Miss Margaret Ball, Mrs. Caryl Boyden, Mrs. Kathleen Cohen, and Mrs. Lourdes Holesko of the Peter Bent Brigham Hospital Surgical Research Laboratory for technical assistance.

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Book Reviews

Reviews in Paediatric Urology. J. Herbert Johnston and Willard E. Goodwin. 482 pages. $49.95. Amsterdam, Elsevier-Exerpta Medica, 1974.

THE EDITORS, in preparing this book, have selected 19 important aspects of pediatric urology and skillfully chosen authors who have a particular interest in that specific content area to review current thinking. This volume of 482 pages, 19 chapters and 26 authors, excellently presents the historical development of these 19 content areas with the authors discussing new developments, clinical management and current criticisms with no obvious bias. For example, the opening chapter entitled "Distal Urethral Stenosis" is by Dr. Richard P. Lyon, who in 1963 published the initial observations on the distal urethral ring. Dr. Lyon, despite his own personal investment in this clinical entity and his advised method of management, accurately records the published criticisms of his methods of diagnosis and treatment.

The opening chapter establishes a criteria of excellence which is generally sustained throughout the book and reflects the editors' care in choosing both subject matter and authorship. The chapter dealing with renal development and the clinical implications thereof effectively establishes the confusion and uncertainty which exists in the area of renal dysplasia and should caution the physician to carefully evaluate the "small kidney" before considering either reconstructive or ablative surgery. The remaining 17 chapters have the advantage of dealing with more clearly defined subject matter and articulate, thoughtful discourse in multiple problem areas is presented. The subjects encompass both benign and malignant disease with careful attention being directed to physiologic mechanisms with accompanying experimental documentation, clinical presentation, evaluation and recommended modes of therapy. The text is precise through the chapters and ambiguity has been avoided by a combination of skillful writing and editing. The chapter on renal transplantation exemplifies this and the reader is presented with an accurate state-of-the-art in pediatric renal transplantation. Dr. Tanagho's following chapter on the pathogenesis and management of megaureter must be considered a classic for its accuracy of presentation both of text and illustration. Each succeeding chapter is of similar quality.

The editors and authors are to be commended on their illustrative materials. Line drawings, photographs and radiographs complement the text throughout and have been precisely reproduced by the publisher. Furthermore, radiographs are reproduced in sufficient size that the reader can appreciate the pathology being demonstrated.

The book is not a textbook in pediatric urology, and the editors do not intend that it be one. However, the range of subject matter (renal transplantation, megaureter, testicular tumors, renal hypertension, urinary tract trauma, calculous disease, chemotherapy, urinary tract infection, cryptorchidism, incontinence, urinary tract reconstruction) effectively scans the problem areas in pediatric urology. The reviews are well referenced, making the text a valuable resource for further review.

DAVID F. PAULSON, M.D.

Dupuytren's Contracture. J. T. Hueston and R. Tubiana. Third edition, 167 pages. New York and London, Crune and Stratton, 1974.

THE THIRD EDITION of this useful book is published in English, the two previous editions (1966 and 1972) having been written in French with English summaries. The observations of 21 of the world's authorities who were members of a study group on the hand have been collated to provide the most complete information on the mysterious and controversial Dupuytren's disease. Various papers, the subjects of 29 chapters, all together numbering 167 pages, contain a very great amount of the total knowledge of this entity and the associated fibrous dysplasias. Although there are overlaps and redundancies, as well as controversial opinions expressed, this book covers all aspects of the subject. Points of agreement and disagreement on modern trends of treatment are discussed and conclusions drawn. This well written and graphically illustrated book should be in the libraries of schools of medicine, hospitals and clinics and be available to surgeons who manage problems of the hand.

DAVID W. ROBINSON, M.D.

Pain Relief. John G. Hannington-Kliff. 178 pages, $15.50. Philadelphia, J. B. Lippincott Company, 1975.

THE AUTHOR, Dr. Hannington-Kiff, has admirably fulfilled his purpose, as he outlined in the preface, on an up-to-date review on the problem of pain relief. I can recommend this book to the student, practitioner and specialist. Its contents include a good discussion on the basic neurophysiological nature of pain with particular emphasis on the gate control theory as well as a concise description of the central integration of pain. The author, rightly so, emphasizes the complex nature of evaluating a patient who has pain, recognizing the emotional, rational, and physical aspects. The chapter on the use of drugs is good as well as that on anesthetic blocks. The relationship of the autonomic system to pain is well discussed and its importance is re-emphasized, a point that has been lacking recently in evaluation of pain problems. Acupuncture is also discussed along with certain forms of exotic oriental treatment. The last half of the book is devoted to the clinical analysis of specific patients with pain problems. The analysis is done on a regional basis, and it is concise and informative. The author is to be commended for a discussion of the new concept of the Pain Clinic using the team approach in analyzing each individual patient.

To me, one of the most interesting parts of the book is the last chapter called "Ahead of Knowledge." Most authors avoid this, but the present one freewheels his thinking, looking ahead to the possible future prospects for better understanding of pain relief. I think it should interest many readers.

The book is good, but the price is not. I would encourage the publisher to produce a less expensive paper covered volume which should encourage widespread use of this new publication.

BLAINE NASHOLD, M.D.

Reactions to Injury and Burns. S. Sevitt. 255 pages, $17.50. Philadelphia, J. B. Lippincott Company, 1975.

DR. SEVITT, the world's leading trauma pathologist, has written a nice overview of the reactions to injury and burns with emphasis on clinical pathological correlation. The chapters on metabolic effects, coagulation and its disturbances after injury, fat embolism, and the lung all deal with subjects in which the author has had long time interest and many valuable insights are provided. The sections on the "sick cell syndrome," described by the Birmingham group, will be of particular interest to all concerned with the care of the severely injured. The careful differentiation between oliguria and renal failure pointing out the etiologic importance of diminished blood flow is especially welcome. The chapter on the lung perhaps unduly emphasizes the role of oxygen toxicity in the etiology of post-traumatic pulmonary insufficiency but provides a thorough review of histologic changes observed in the lungs of injured man. The chapter on cellular and humoral immunity correlates splenic and lymph node changes with peripheral blood element changes and rightly questions the importance of reticuloendothelial system changes as related to infection in trauma patients.

The illustrative material is uneven and the use of color illustrations would have improved their effectiveness. The selection of case material is also spotty—the use of a patient (Fig. 5.5) with inhalation injury who received 100% oxygen for only a few hours to exemplify oxygen toxicity is puzzling. Puzzling also is the complete omission of the gastrointestinal tract as is the brief and rather disorganized consideration of sepsis, the most common cause of death in severely injured patients. The general paucity of pathology emphasis and specimen photographs with concentration on, at times unfounded, physiologic speculation by this experienced pathologist is paradoxical. Nevertheless, the book does represent the best treatise available on the pathology of trauma available today and as such, will be of interest to house officers and practicing physicians concerned with the care of injured man. The references and bibliography provide a strong historical background, but important, more current work is both uncited and neglected in the text. It is hoped that in the next edition, Dr. Sevitt will concentrate on his area of greatest strength, a complete and detailed description of the gross and microscopic organ changes which are so important in determining the response and ultimate outcome of severe injury.

BASIL A. PRUITT, JR., M.D.

Sudden Death and Coronary Disease. Sidney Goldstein, M.D. 224 pages, $15.00. New York, Futura Publishing Company, Inc., 1974.

THIS IS A VERY FASCINATING and highly readable monograph concerning a topic of much interest. The author, who is Chief of the Division of Cardiovascular Diseases at Henry Ford Hospital, is eminently qualified to undertake this task.

The importance of sudden death and its relation to coronary artery disease is emphasized by stark statistics in that some 600,000 U. S. citizens die annually from complications of coronary artery disease. Of particular significance is the fact that approximately half of this group die *suddenly*. The entire subject is thoroughly reviewed beginning in 1901 with a quotation from Krehl, a leading figure in German medicine, who said of coronary disease: "Occlusion is compatible with survival; the patient survives unaware of the abyss which he has crossed." The early work in recognition of coronary artery disease and its relationship to sudden death was initiated by two Russian clinicians, Obrastzow and Straschesko, who in 1910 reported early clinical observations. These contributions were soon followed by those of Herrick of Chicago, who in 1912 made the first clinical diagnosis of acute myocardial infarction.

The pathology of sudden death is reviewed and it is stated that the incidence of thrombotic occlusion of coronary arteries in acute myocardial infarction has varied from 7 to 91% in postmortem studies. However, it is recognized that thrombosis is more apt to occur in those patients who survive for a longer period. For example, in one series of patients whose death from coronary heart disease occurred in less than one hour, only 16% had thrombotic occlusion whereas the incidence of thrombosis rose to 54% in those who survived one day or longer in the hospital. In patients dying less than one minute after onset of symptoms, it was found that total obstruction of two or more coronary arteries was 7 times as frequent than those whose death occurred from one minute to 24 hours after the onset of symptoms. The author emphasizes that hypercholesterolemia (serum cholesterol greater than 250 mg), hypertension (diastolic pressure greater than 90 mm Hg), and cigarette smoking in any amount are each factors of proven importance. Data are cited which show that the presence of any one or a combination of these increase the risk of death from myocardial infarction. An interesting chapter is devoted to the topic of "Medical Treatment and Prevention" as well as chapters on mechanism of death and relationship of sudden death to exercise.

In summary, this is a very fascinating monograph, concisely written in less than 200 pages. It is the source of much important and timely data of interest to all in medicine. As Michael F. Oliver of the University of Edinburgh states in the Introduction to this text, "This valuable monograph assembles information from which we should be able to make the next moves to discover how to predict and prevent sudden death. It also provides the facts to enable us to reappraise Macbeth's "strange images of death."

DAVID C. SABISTON, JR. M.D.

Trauma Management. E. F. Cave and Associates. 1,237 pages. Chicago, Yearbook Medical Publishers, 1974.

THIS VOLUME is a treatise of 1,237 pages and 54 chapters. This large and authoritative textbook constitutes the reabridged edition of "Fractures and Other Injuries" by Dr. E. F. Cave.

The prime criticism and yet at the same time, the outstanding feature of this book is the fact that it is not a general textbook of trauma management but is basically a very detailed book fracture management. Of the 54 chapters, 38 are devoted to management of trauma to bones, joints, ligaments, and tendons. These constitute a very detailed, up-to-date and authoritative review of the management of specific orthopedic problems.

The 16 chapters on Trauma other than orthopedics consist of an excellent chapter on metabolic response to trauma, early examination and treatment of the injured patient, shock, sepsis, soft tissue repairs, chest injuries and cardiac trauma, abdominal injuries, pheripheral vascular injuries and burns. These chapters generally would provide excellent review for the orthopedist but would be disappointing to many general surgeons who purchase the text as a detailed review of trauma.

I would endorse the book to be an excellent reference source for Orthopedic Trauma but feel that more comprehensive texts on general aspects of trauma are available elsewhere.

F. WILLIAM BLAISDELL, M.D.

Progress in Clinical Immunology. Two volumes, R. S. Schwartz, M.D.

THIS VOLUME contains seven chapters devoted to areas of special current interest. The first chapter is "Immunodeficiency: Enigmas and Speculations" and briefly defines several of the well known immunological deficiency syndromes. The second chapter, "Clinical Applications of *In Vitro* Lymphocyte Tests," by Röcklin is excellent. The author reviews the most commonly used *in vitro* lymphocyte tests and describes how they have been used in characterizing various immunodeficiency states ranging from Di George's syndrome to drug hypersensitivity. There is an extensive review of the literature; this chapter alone has 272 references. The third chapter, "Therapeutic Uses of Transfer Factor," is also excellent and describes the present knowledge of the transition of cell-mediated immunity reactions from one individual to another, using dialyzable transfer factor. In the fourth chapter, "Autoimmunity and Lymphoid Malignancy in New Zealand Black Mice," Tadal describes investigations with this fascinating animal which seems to be an experimental model for at least three different human diseases, systemic lupus erythematosis, Sjogren's syndrome, and Waldenstrom's macroglobulinemia. Chapter 5, "Surface Immunoglobulins on Human Lymphoid Cells," by Preud'Homme and Seligmann, is of high quality and again the literature is exhaustively reviewed, there being over 300 references in the bibliography. The sixth chapter is on "Complement in Immunohematology" by Pitts and Garratty, and the seventh is on a current topic of exceeding interest, "Carcinofetal Antigens," by Costanza and Nathanson.

Generally, this is an excellent volume, and for the topics covered offers thorough reviews of the literature. Most chapters should serve as an excellent resume and reference source for medical students, basic investigators, and clinical immunologists. In surgery, it will mostly appeal to those in the transplantation and tumor immunology fields.

SAMUEL A. WELLS, JR, M.D.

Letters to the Editor

September 3, 1975

Dear Editor:

I feel compelled to comment on the article entitled "Occult Inguinal Hernia in the Female," by Jack K. Herrington, M.D.

Dr. Herrington seems to be suggesting that hernias can be accurately diagnosed by history alone. His evidence seems to be the finding of a patent canal of Nuck at the internal ring. The figures that he quotes of 8–10%, 18%, and 25% patency in "normal" individuals should discount the importance of this finding.

The placebo effect of surgery has been well documented, e.g., internal mammary ligation for angina pectoris. I don't think, therefore, that patient satisfaction is justification either.

A hernia is a physical finding which should be demonstrated prior to herniorrhaphy.

Edward J. Flynn, Jr., M.D.
1500 South Avenue D
Portales, New Mexico 88130

September 30, 1975

Dear Editor:

In response to Dr. Edward J. Flynn's comments concerning "Occult Inguinal Hernia in the Female," an element of controversy is not unexpected. The essential concept proposed is new. For precisely this reason publication of the work was delayed to cover a 5-year experience. This experience established the validity of a syndrome which most certainly does exist, but is not commonly recognized in the surgical world. I am confident that careful evaluation of the manuscript satisfactorily addresses itself to the questions that it most certainly raises.

More specifically, it must be pointed out to Dr. Flynn that the paper does not suggest that "hernias can be accurately diagnosed by history alone," but rather a small group of female patients can be so diagnosed when other diagnostic possibilities are ruled out. Furthermore, the manuscript does not refer to patency rates of the Canal of Nuck in "normal" individuals, but rather to rates determined by painstaking anatomic studies by investigators who do not address themselves to the clinical significance of these facts. The patients in this study are not normal patients, but rather individuals with significant inguinal pain brought on by exertion. These individuals desire careful scrutiny and appropriate therapy as suggested. It is difficult to accept the "placebo effect" when indirect fascial defects and hernia sacs are indeed found and corrected.

Jack K. Herrington, M.D.
Chief of Surgery
Deaconess Hospital
Milwaukee, Wisconsin 53233

January 6, 1975

Dear Editor:

Drs. Feldstein et al.[1] report the first proven case of mumps hemorrhagic pancreatitis in a child. However both the title and the test of their report seem to suggest that the complication of pseudocyst formation is also secondary to the mumps infection. Isn't it more likely that the pseudocyst is secondary to the trauma of the first exploratory operation and especially to the trauma of manipulation of the pancreas at surgery (e.g. for the photographs)?

Glenn C. Szalay, M.D.
Southern California
Permanente Medical Group

Reference

1. Feldstein, J. D., Johnson, F. R., Kallick, C. A., and Doolas, A. D.: Acute Hemorrhagic Pancreatitis and Pseudocyst Due to Mumps. Ann. Surg., 180:85, 1974.

January 10, 1975

Dear Editor:

Dr. Szalay believes that the pseudocyst in the child with mumps did not result from the already existing hemorrhagic pancreatitis, but rather from our exposure of the pancreas through the gastrocolic omentum for the purpose of draining the lesser sac. We believe that the pseudocyst developed after the drains were inadvertently dislodged early in the postoperative course, thus allowing the lesser space to accumulate fluid. If further damage had been caused during the drainage procedure, we would have expected the patient to have deteriorated rather than improve immediately as he did.

Alexander Doolas, M.D.
1725 West Harrison Street
Chicago, Illinois 60612

November 24, 1975

Dear Editor:

In reply to the letter by Dr. K. Sukarochana in regard to the problem of plastic drapes causing retention of temperature, the statement made in my article did not refer to our own work, but referred to the work done by the same investigators as were quoted in Dr. Sukarochana's article. However, to make sure that Dr. Sukarochana and I are talking about the same thing, I must emphasize two points.

First, in our article, we mentioned the well-known fact that plastic-laminated nonwoven materials retain heat. The material tested by Dr. Sukarochana is not such a laminated material, but is a spread tow plastic film composite, actually the same material which our tests proved to be quite effective in preventing moist bacterial strike-through.

Second, in Dr. Sukarochana's paper, he refers to the nonwoven drape material he tested for heat retention as being nonporous. Actually, spread tow plastic film composite does have a porosity, but it is fine enough not to permit moist strike-through, but does permit some air exchange, and therefore does not cause rapid heat retention.

Harold Laufman, M.D.
Montefiore Hospital and Medical Center
111 East 210th Street
Bronx, New York 10467

August 22, 1975

Dear Editor:

Your publication of an article by Harold Laufman titled "Strike-through of Moist Contamination by Woven and Nonwoven Surgical Materials" which appeared in the Annals of Surgery in June of 1975 was interesting. The comment of the author on page 862 in regard to the temperature problem of the plastic adhesive or the plastic drape is not quite consistent with our finding.

Our article, "A Nonporous Fabric Drape" which appeared in the Journal of Archives of Surgery, Volume 99, July 1969, demonstrated that the fabric drape does not produce or retain body temperature and has not had any adverse affect in this regard, especially in the pediatric age group.

Kamathorn Sukarochana, M.D.
Perry Medical Corporation
9066 Perry Highway
Pittsburgh, Pennsylvania 15237

November 7, 1975

Dear Editor:

The paper by Warsaw et al., in the October 1975 issue of the Annals of Surgery, speculates on the possible role of circulating lipids in the genesis of pulmonary edema in acute pancreatitis.

The edema they describe is whole plasma lost from the circulation as a result of capillary injury that others describe as "shock lung" or "acute respiratory insufficiency." They are content to limit the therapeutic objective to intensive respiratory support and prevention of pulmonary infection. This therapy often fails because it does not come to grips with the etiological agent. One cause of the syndrome that has been demonstrated in man as well as the experimental animal is endotoxemia of intestinal origin (identified by the limulus lysate test). Acute pancreatitis is a disorder in which vasoactive agents are released. These increase the permeability of the gut and so induce an endotoxemia when the RE system fails to keep pace with the load of endotoxin being absorbed.

Jacob Fine, M.D.
Veterans Administration Hospital
Boston, Massachusetts 02130

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December 9, 1975

Dear Editor:

Dr. Fine, in his letter concerning our paper describing the pathogenesis of pulmonary edema in acute pancreatitis, appears to lump that entity together with other forms of "acute respiratory insufficiency." Inasmuch as there may be many similar clinical entities with different pathogeneses, different hemodynamics, and different natural histories, we do not think that such lumping serves a useful or valid purpose.

Dr. Fine then goes on to say that therapy for these conditions consisting of intensive respiratory support and prevention of pulmonary infection, often fails. An important point of our paper, however, is that such therapy was always successful in our experience with the pulmonary edema associated with acute pancreatitis. Obviously other forms of "acute respiratory insufficiency" do not always respond as well, and therapy must be given for whatever underlying factors, such as sepsis or fat embolism, can be identified.

Dr. Fine's speculations about the role of endotoxemia in human disease states have long been of great interest. The relevance of such speculations in acute pancreatitis is not known, nor is the reliability of the limulus lysate test generally accepted as reliable evidence of endotoxemia in man. In any case, most of the patients in this series received antibiotic therapy appropriate to enteric bacteria.

Andrew L. Warshaw, M.D.
Paul B. Lesser, M.D.
Michael A. Rie, M.D.
David J. Cullen, M.D.
Department of Surgery
Massachusetts General Hospital
Boston, Massachusetts 02114

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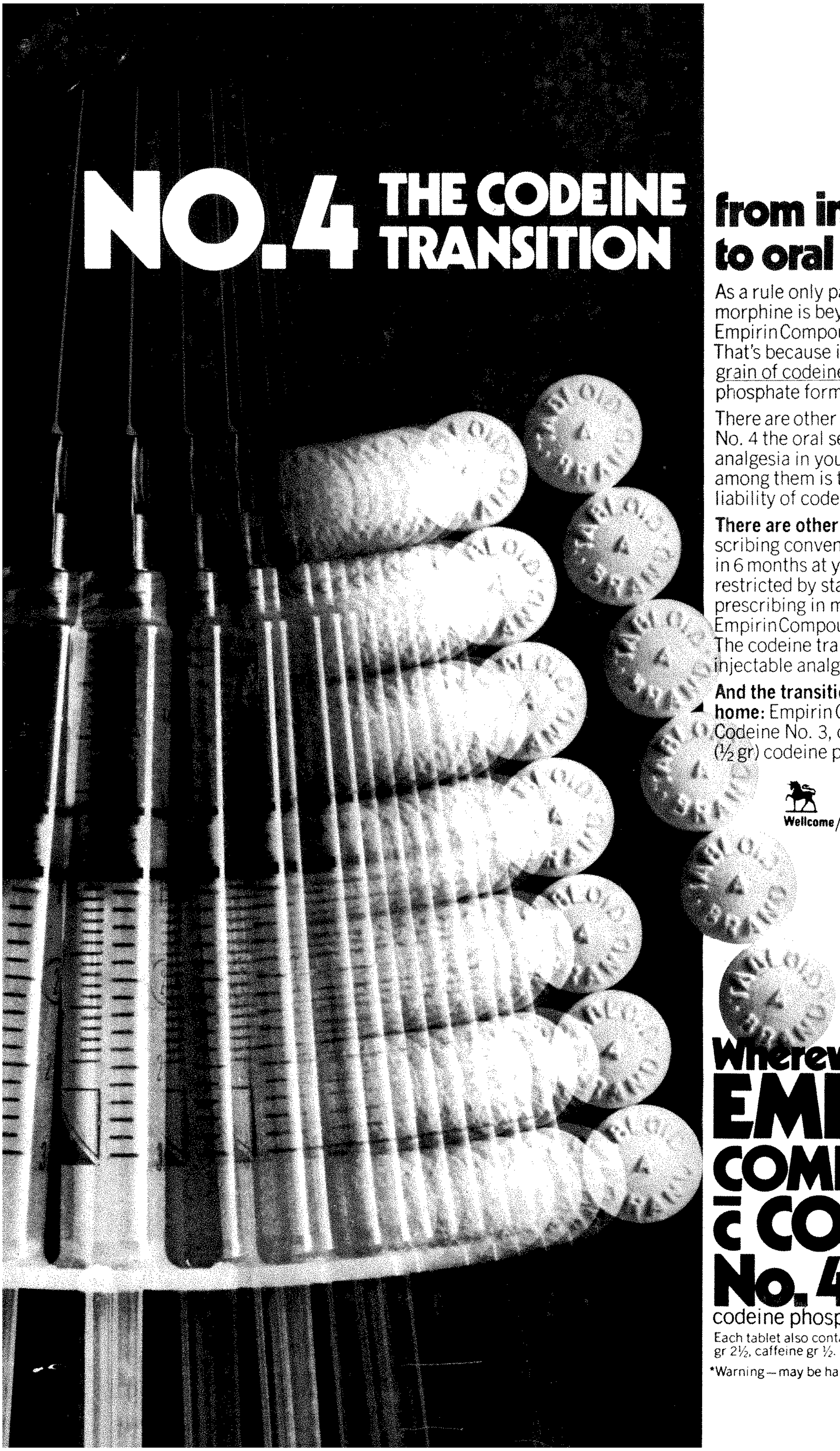

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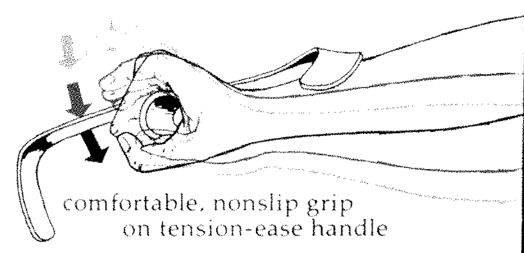
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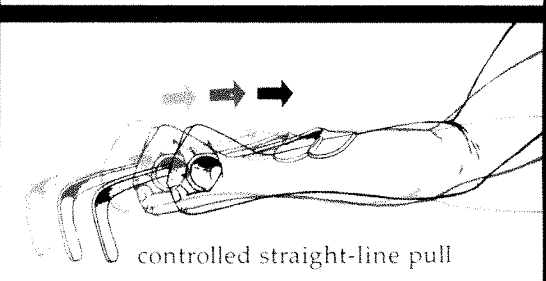
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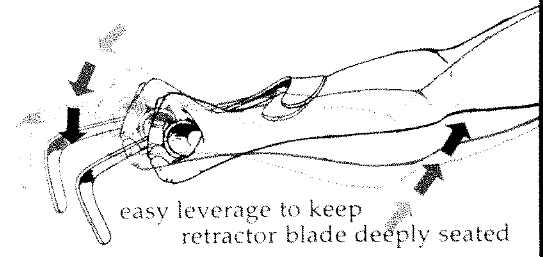
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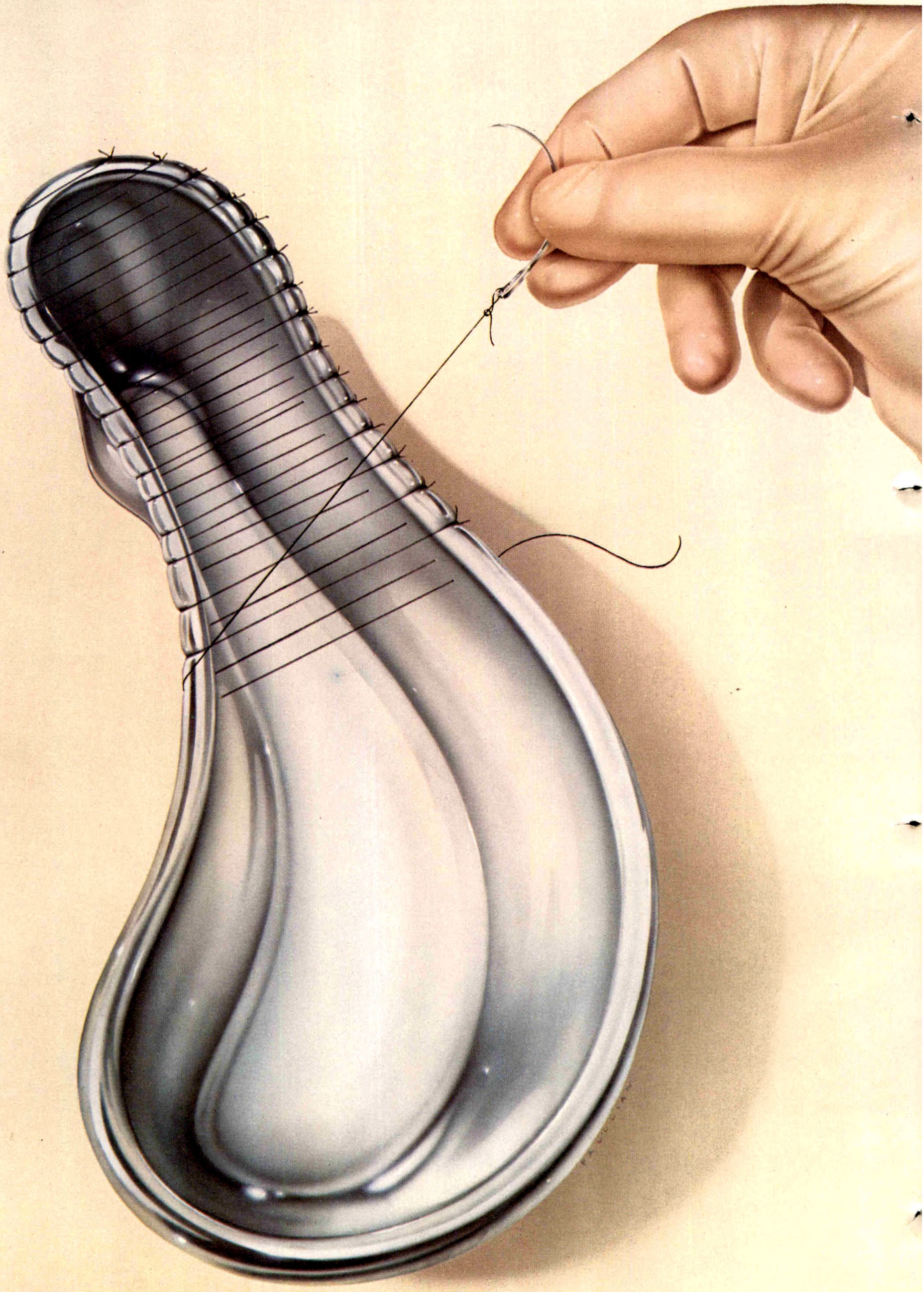

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REFERENCES:
1. Zauder, H. L., et al.: Prophylaxis of postoperative emesis. Scientific Exhibit presented at 122nd Annual Convention of the American Medical Association, New York, June 23-27, 1973.
2. Lutz, H., and Immich, H.: Curr. Ther. Res. *14*:178, April, 1975.
3. Steen, S. N., and Yates, M.: Anesthesiology *36*:519, May, 1972.

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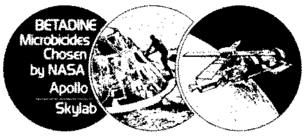
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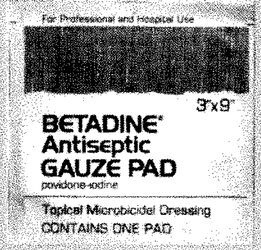

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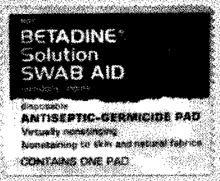

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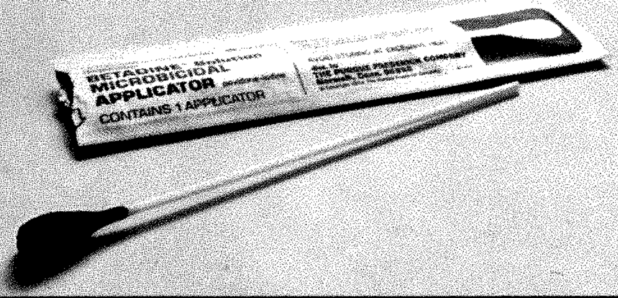

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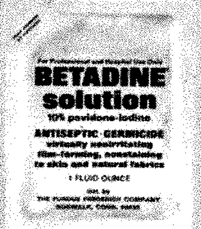

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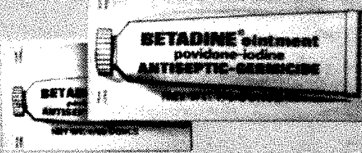

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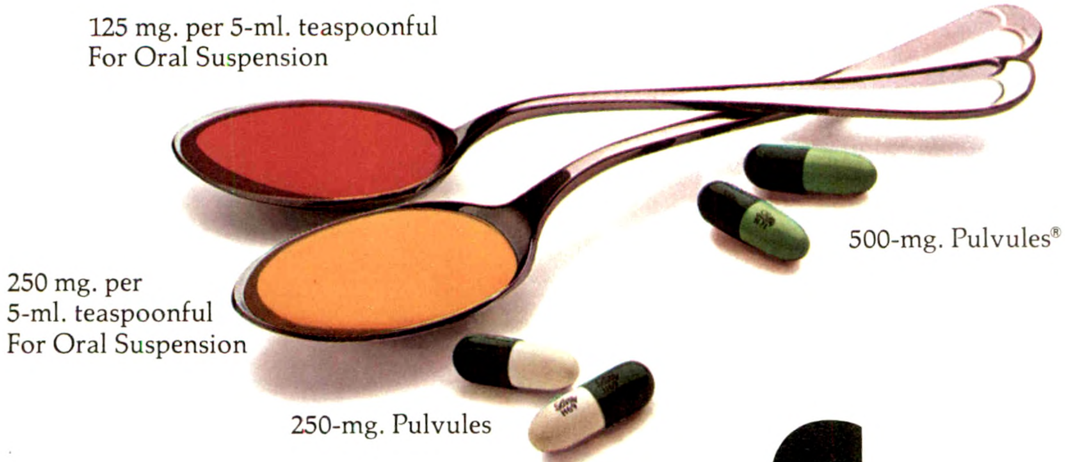

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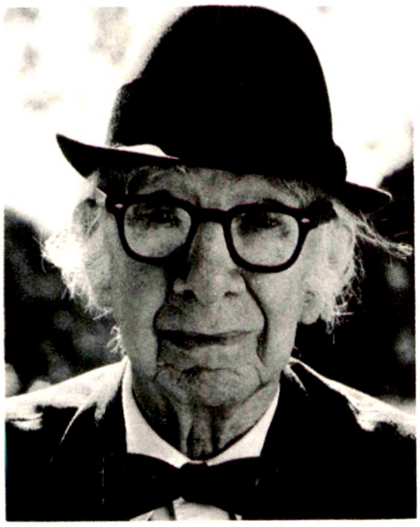

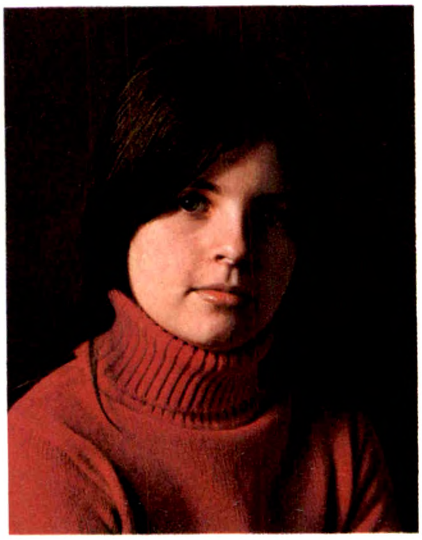

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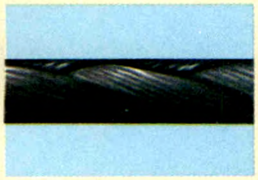

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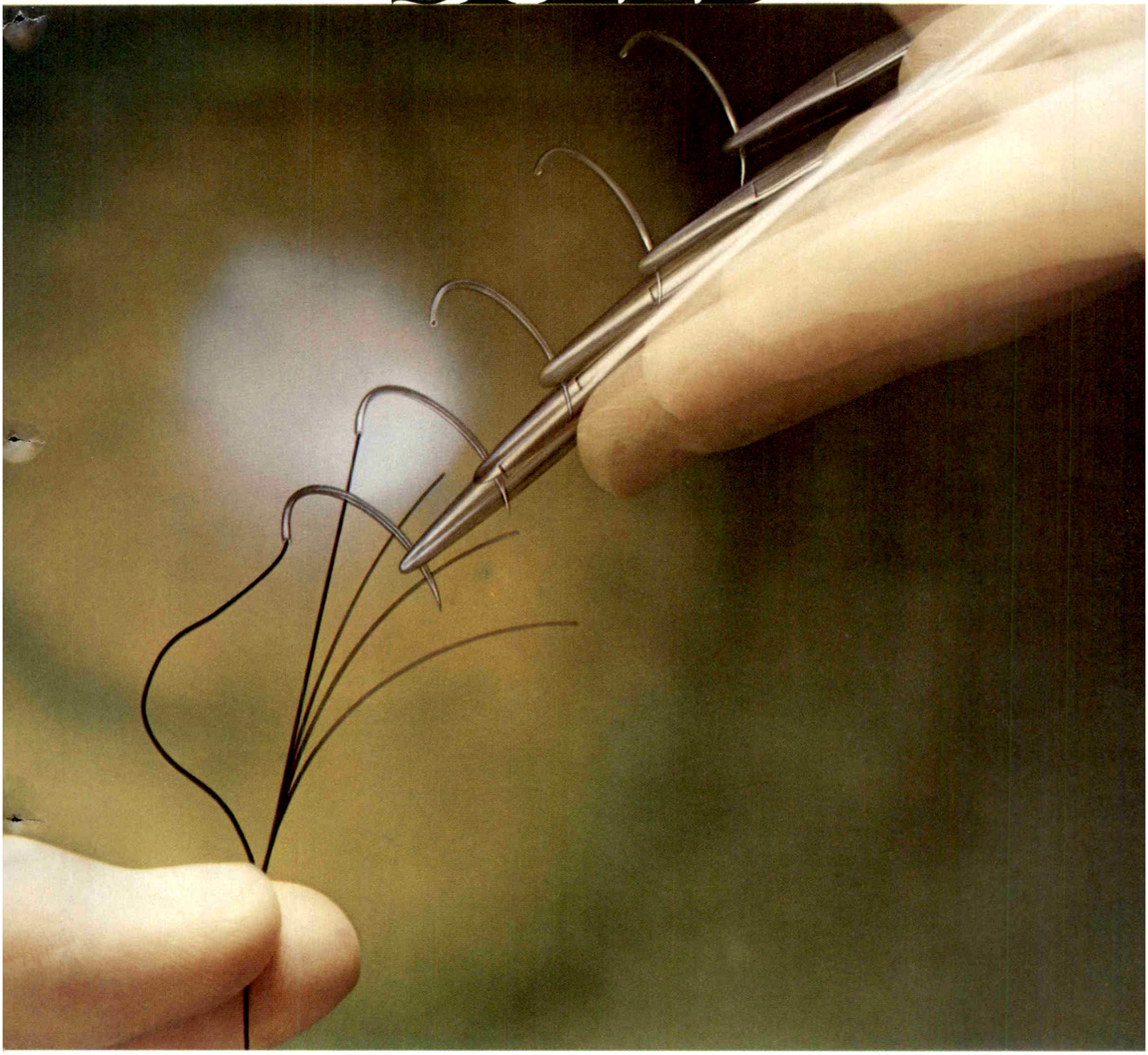

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Joint treatment against staph*:

Injection and tablets Unipen® (nafcillin sodium)

AS THE MONOHYDRATE,BUFFERED,WYETH

Postoperative surgical infections
Recent advances in surgical technique have been so remarkable that now total joints can be replaced with prosthetic devices. But the introduction of foreign materials—protheses, pins, nails, screws—designed to replace damaged parts or facilitate healing, can often lead to infection. Commonly, the implicated organism will be a penicillinase-producing staph. Progression can be swift and devastating.

Initial antistaph therapy: injection
It's vitally important that effective treatment of bacterial invasion begin as soon as possible. If you suspect the presence of staph and must begin therapy before definitive culture results are known, Injection Unipen® (nafcillin sodium)† is a particularly suitable agent.

Appropriate specimens for bacteriologic studies to determine the causative organisms and their susceptibility to nafcillin should be taken prior to the first dose of antibiotic.† And, if those studies subsequently implicate organisms other than penicillinase-producing staphylococci sensitive to nafcillin, discontinue it and administer the appropriate antibiotic.

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Unipen appears rapidly in plasma following intramuscular administration. Penetrates body tissues in high concentration and diffuses well into pleural, pericardial and synovial fluids.

"On call" capability
Reconstitutes in less than 60 seconds. Remains stable for 24 hours.‡

Follow-up therapy: tablets
Unipen is available in tablet form as well as parenteral. So the injectable form can be used initially in severe infections. And as soon as the clinical condition warrants, Unipen tablets allow you to continue antistaph therapy with the same antibiotic in a form more agreeable to most patients.

*Nafcillin-susceptible penicillinase-producing staphylococci.
†See Important Note on next page.
‡See important information under Parenteral Administration on next page.

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See important information on next page.

Unipen®
(nafcillin sodium)

AS THE MONOHYDRATE, BUFFERED, WYETH

Disc Susceptibility Tests: Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure* has been recommended for use with discs for testing susceptibility to penicillinase-resistant penicillin-class antibiotics. Interpretations correlate diameters on the disc test with MIC values for penicillinase-resistant penicillins. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used, or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

*Bauer, A.W., Kirby, W.M.M., Sherris, J.C., and Turck, M.: Antibiotic Testing by a Standardized Single-Discs Method, Am. J. Clin. Pathol., 45:493, 1966; Standardized Disc Susceptibility Test, FEDERAL REGISTER 37:20527-29, 1972.

Indications: Although the principal indication for nafcillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to nafcillin sodium should be performed.

In serious, life-threatening infections, oral preparations of the penicillinase-resistant penicillins should not be relied on for initial therapy.

Important Note: When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of nafcillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to nafcillin sodium, the physician is advised to continue therapy with a drug other than nafcillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Methicillin is a compound that acts through a mechanism similar to that of nafcillin sodium against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in **in vitro** sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

Contraindications: A history of allergic reaction to any of the penicillins is a contraindication.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, appropriate therapy should be instituted, and discontinuation of nafcillin therapy considered. The usual agents (antihistamines, pressor amines, corticosteroids) should be readily available.

Precautions: As with any potent drug, periodic assessment of organ system function, including renal, hepatic and hematopoietic, should be made during prolonged therapy.

The possibility of bacterial and fungal overgrowth should be kept in mind during long-term therapy. If overgrowth of resistant organisms occurs, appropriate measures should be taken.

The oral route of administration should not be relied upon in patients with severe illness, or with nausea, vomiting, gastric dilatation, cardiospasm or intestinal hypermotility.

Safety for use in pregnancy has not been established.

Particular care should be taken with intravenous administration because of the possibility of thrombophlebitis.

Adverse Reactions: Reactions to nafcillin sodium have been infrequent and mild in nature. As with other penicillins, the possibility of an anaphylactic reaction or serum sickness-like reactions should be considered. A careful history should be taken. Patients with histories of hay fever, asthma, urticaria, or previous sensitivity to penicillin are more likely to react adversely.

The few reactions associated with the intramuscular use of nafcillin sodium have been skin rash, pruritus, and possible drug fever. As with other penicillins, reactions from oral use of the drug have included nausea, vomiting, diarrhea, urticaria, and pruritus.

Parenteral Administration: It is recommended that parenteral therapy be used initially in severe infections. The patient should be placed on oral therapy with this product as soon as the clinical condition warrants. Very severe infections may require very high doses.

Intravenous Route: The required amount of drug should be diluted in 15 to 30 ml. of Sterile Water for Injection, U.S.P., or Sodium Chloride Injection, U.S.P., and injected over a 5- to 10-minute period. This may be accomplished through the tubing of an intravenous infusion if desirable.

Stability studies on nafcillin sodium at concentrations of 2 mg/ml and 30 mg/ml in the following intravenous solutions indicate the drug will lose less than 10% activity at room temperature (70° F.) during the time period stipulated:

Isotonic sodium chloride	24 hours
5% dextrose in water	24 hours
5% dextrose in 0.4% sodium chloride solution	24 hours
Ringer's solution	24 hours
M/6 sodium lactate solution (conc. of 30 mg/ml)	24 hours

Discard any unused portions of intravenous solutions after 24 hours.

Only those solutions listed above should be used for the intravenous infusion of Unipen® (nafcillin sodium). The concentration of the antibiotic should fall within the range of 2 to 30 mg/ml. The drug concentrate and the rate and volume of the infusion should be adjusted so that the total dose of nafcillin is administered before the drug loses its stability in the solution in use.

There is no clinical experience available on the use of this agent in neonates or infants for this route of administration.

This route of administration should be used for relatively short-term therapy (24-48 hours) because of the occasional occurrence of thrombophlebitis, particularly in elderly patients.

Intramuscular Route: The clear solution should be administered by deep intragluteal injection immediately after reconstitution. After reconstitution, keep refrigerated (2°-8° C.) and use within 7 days or keep at room temperature (25° C.) and use within 3 days.

Oral Administration: Beta-hemolytic streptococcal infections should be treated for at least 10 days to prevent development of acute rheumatic fever or glomerulonephritis.

If oral therapy is inadequate, resort to parenteral nafcillin sodium.

After mixing, the oral solution must be stored in a refrigerator. Discard any unused portion after one week.

Supplied: INJECTION (VIALS)—Supplied in vial sizes of 500 mg., 1 gram, and 2 gram nafcillin sodium as the monohydrate, buffered. When reconstituted as recommended, the contents of each vial provides, respectively, 2-, 4- or 8-ml. of nafcillin sodium solution equivalent *per ml.* to 250 mg. nafcillin buffered with 10 mg. sodium citrate. Film-coated TABLETS—containing nafcillin sodium as the monohydrate, equivalent to 500 mg. nafcillin buffered with calcium carbonate. CAPSULES—containing nafcillin sodium, as the monohydrate, equivalent to 250 mg. nafcillin buffered with calcium carbonate. FOR ORAL SOLUTION—Combination pkg. of vial of dry nafcillin sodium as monohydrate and bottle of diluent—provides 80 ml. of solution containing equivalent of 250 mg. nafcillin per 5 ml. Alcohol 2%.

WYETH LABORATORIES PHILADELPHIA, PA.

ANNALS OF SURGERY

Vol. 183 May 1976 No. 5

Presidential Address:

Societies, Surgeons and Surgery

WILLIAM H. MULLER, JR., M.D.

From the Department of Surgery,
University of Virginia Medical Center,
Charlottesville, Virginia 22901

ONE HAS ONLY TO OBSERVE a list of medical society meetings projected for the next year to become enormously impressed with the great number of state, regional, national and international organizations which bring members of the medical profession together at regularly scheduled intervals. I have long been interested in the reasons and purposes for the origin and development of societies and I wish to examine and elaborate upon some of the influences they have had on surgeons and surgery in this country.

Since the emergence of surgery from barbarism and throughout its development to present-day standards of achievement, surgeons as well as those in other fields of medicine have sought organization for various purposes. The charter granted in 1505 by King James IV of Scotland (Fig. 1) incorporating the barber surgeons of Edinburgh might be considered the basis of the first surgical society in the English-speaking world. Indeed, the Royal College of Surgeons of Edinburgh (Fig. 2) derives its status as the oldest surgical corporation in the British Commonwealth by virtue of its unbroken descent from this charter. It is well-known that James IV expressed great interest in scientific affairs, and Sir John Bruce states that he was "well learned at the art of medicine and also a cunning Chirurgener that none in his realm that used that craft but would take his counsel in all their proceedings."[1] James would also pay his subjects for the opportunity of trying his own hand at their surgical care. A similar charter was granted by Henry VIII to the barber surgeons of London and England, and Queen Victoria subsequently granted a charter to the Royal College of Surgeons in 1843. These charters and the organizations they fostered were of immense importance because they recognized surgery as a scientific section of medicine, and served to exclude barbers, cultists and others from practicing surgery legally.

Throughout the centuries numerous organizations have risen, declined and fallen, many of the reasons for which are clearly recorded in an excellent report by C. Rollins Hanlon.[2] Each was established for purposes often fulfilled, but sometimes not, and often made a contribution which was desired or needed at the time. While many of these purposes and goals have remained steadfast since scientific societies originated, new ones have been added and existing ones expanded as roles and obligations of the day demanded.

Renaissance Italy is generally credited with originating scientific societies, and it has been traditional to trace their lineage to Plato's famous academy. They spread across Europe in the 17th century, spanning the Atlantic Ocean to this country in the 18th and 19th centuries. They were born as a result of man's basic desire to increase his knowledge of nature, and have served as some of the most effective instruments for increasing and diffusing the world's store of knowledge. Certainly they have served to stimulate scientific advancement tremendously in America. Scientific societies preceded true medical and surgical societies in this country by more than a century, and it is interesting to examine some of them briefly. The first was the learned Boston Philosophical

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Presented at the Annual Meeting of the Southern Surgical Association, December 8–10, 1975, The Homestead, Hot Springs, Virginia.

FIG. 1. James IV of Scotland (Courtesy of the James IV Association of Surgeons).

Society around 1680. It was later described by Cotton Mather as "a philosophical society of agreeable gentlemen who met once a fortnight for a conference upon improvements in philosophy and additions to the stores of natural history." But, alas, it was shortlived, because Boston became involved in political and theological disputes, referred to in those days as "the calamity of the times," and the study of science became a sideline; however, during the 18th century the tenor and environment for the study of science in America became much more favorable. Newtonian philosophy and the early beginnings of the scientific revolution in Europe and particularly France began to find their ways into the thinking of some of the more intellectual colonists. According to Bates,

> "There was one city in America whose citizens were especially prepared to receive the new leavening influence, and that was Philadelphia. From the time of its founding, the 'City of Brotherly Love' had been a haven to all of liberal tendencies and bold, inquiring turn of mind. Its cosmopolitan population comprised all manner of intellects and it kept them supplied by the outpourings of thriving printeries."[3]

Philadelphia was moreover an important medical center. It was quite natural, therefore, that it should be the scene of the next American scientific society.

Finding none when he migrated from Boston to Philadelphia, young Benjamin Franklin decided to initiate one himself and in 1727 formed the Junto, a secret literary and scientific group. (Fig. 3) Although it apparently functioned successfully, he realized the need for a more comprehensive and influential organization, and in 1743 he circulated a letter entitled "A Proposal for Promoting Useful Knowledge in the British Plantations in America." Thus the American Philosophical Society was created. It should be pointed out that the word "philosophical" had a meaning in Franklin's day different from its current use. It was defined then as a systematic study of practically any category of phenomena. Many members of the new society therefore discussed a wide scope of subjects including natural philosophy, moral science, history and politics, and they performed investigations in botany, medicine, many of the physical sciences, mechanics, art and a host of other fields. Franklin encouraged correspondence from distant members and outlined a long list of appropriate subjects, ranging from new mechanical inventions for labor saving to improvements of vegetable juices, and concluded the list with "and all philosophical experiments that let light into the nature of things, tend to increase the power of man

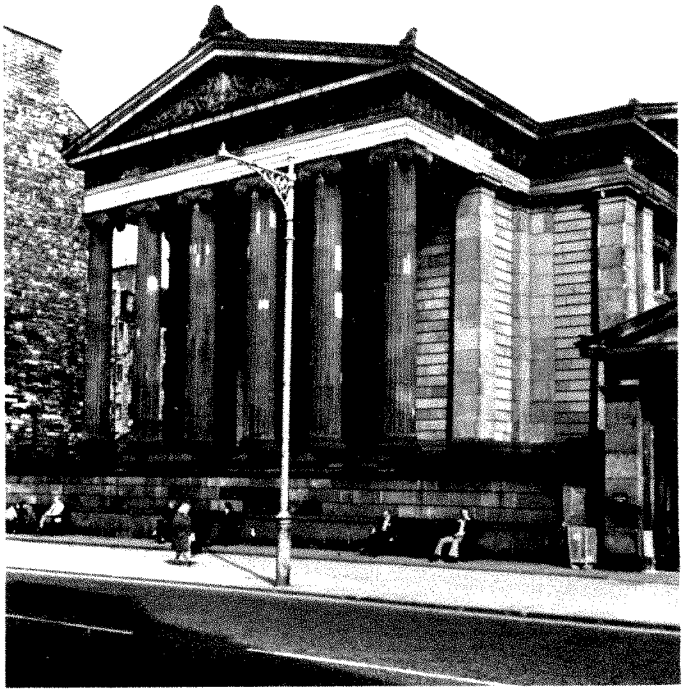


FIG. 2. Royal College of Surgeons Building, Edinburgh, Scotland.

over matter, and multiply the conveniences and pleasures of life." The influence of that society is legend and many members of this Association have undoubtedly visited the imposing Philosophical Hall, erected in 1789 upon land granted by the Commonwealth of Pennsylvania. (Fig. 4)

Not only did the American Philosophical Society have a tremendous influence upon the development of science in America, but it exerted an influence on science in Europe as well. Franklin states that in France among the academicians and other men of science and letters, questions were frequently asked concerning the Philosophical Society of Philadelphia, and praise was often extended for some of the publications in its "Transactions." He states that this suggested to him the idea of such an establishment at Boston, where "I knew there was as much love of science and as many gentlemen who were capable of pursueing it as in any other city of its size." He visited Boston in 1779 and was seated next to Samuel Cooper at a dinner in honor of the French Ambassador. Franklin interested Dr. Cooper so greatly in the idea of a Massachusetts Institute and Academy of Arts and Sciences that, through the doctor's vigorous efforts, the proposal was brought before the state legislature, and the charter of incorporation was written the following year, 1780, for the American Academy of Arts and Sciences. Governor James Bowdoin of Massachusetts became the first President, and prominent men throughout the country, including John and Samuel Adams, John Hancock, George Washington, Benjamin Franklin, David Rittenhouse, and Thomas Jefferson, became members. In addition, the esteemed foreign honorary members included many prominent European scientific and political figures of the day.

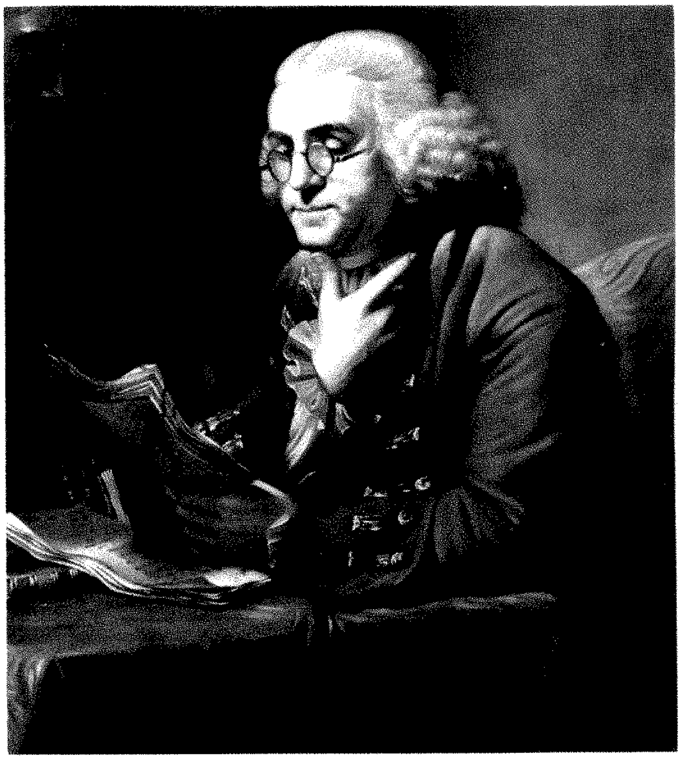


FIG. 3. Benjamin Franklin, 1787, by C. W. Peale (Courtesy of the American Philosophical Society).

One of the most interesting and ambitious schemes to develop a scientific academy was an attempt under French guidance to establish at Richmond, Virginia, in 1788 an institution similar to the Academy of France, with branch academies in Baltimore, Philadelphia and New York. Correspondence and exchange with the great learned and scientific societies of the Old World were also planned. The perpetrator of this bold enterprise was Chevalier Quesnay, the son of a noted French economist. He had served in the American Revolution along with Lafayette, but was forced by illness to give up his military career. John Page, then the Lieutenant Governor of Virginia, suggested to him the idea of an Academy in America and urged him to bring European professors to this country. The promise of help in securing the Presidency of the Academy encouraged Quesnay to campaign for the project, and many prominent Virginians, as well as subscribers in other colonies, are said to have given large sums of money. The new Academy of the United States of America was to comprise an elaborate organization of an impressive local faculty and a large number of nonresident associates representing the best scholarship of the old and new worlds. Quesnay himself returned to Paris and obtained the approval of the King and Queen, as well as that of all the important agencies, including the Royal Academy of Sciences and the Royal Academy of Painting and Sculpture. Tentative arrangements were made for establishing in Virginia advanced schools offering courses in virtually every field.

The project speedily collapsed, however, because Quesnay was detained in Europe by family affairs, aid from France was withdrawn at the outbreak of the French Revolution, and the scattered population of rural Virginia had not been sufficiently aroused to provide financial support. It is interesting to speculate as to what might have happened if the Academy had achieved success. One scholar states,

> ". . . if circumstances had favored Quesnay's project, it is probable that the University of Virginia would never have been founded. There would have been no need for it. The Academy of the United States of America, established at Richmond, would have become the center of higher education, not only for Virginia, but for the whole South, and possibly a large part of the North, if the Academy had been extended as proposed, to the cities of Baltimore, Philadelphia, and New York. Supported by French capital, . . . strengthened by French prestige, and by literary, scientific and artistic associations with Paris, then the intellectual capital of the world, the Academy at Richmond might have become an intellectual stronghold, comparable in some degree to the Jesuit in Canada, which has

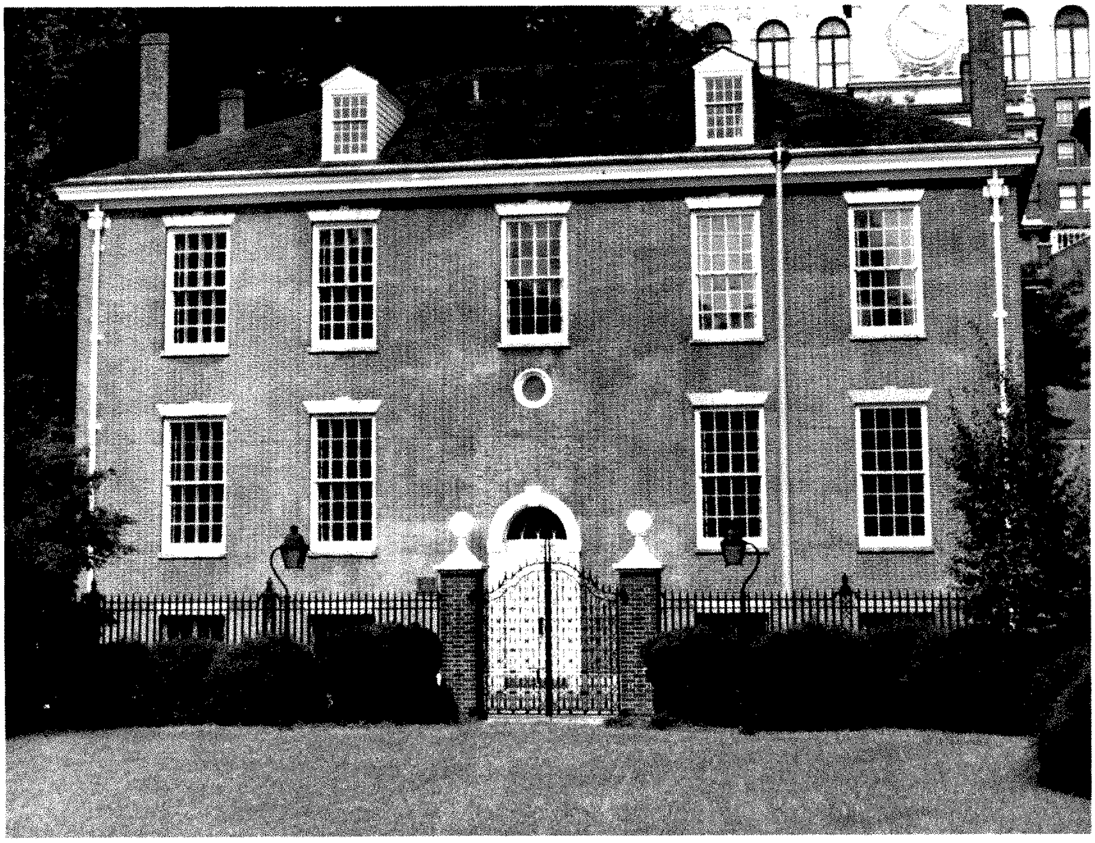


FIG. 4. American Philosophical Society Hall, Philadelphia (Courtesy of the American Philosophical Society).

> proved more lasting than French dominion, more impregnable than the fortress of Quebec."[4]

Its influence may not have been entirely lost, however, because its aims and objectives and its plan for graduate instruction were well known to Thomas Jefferson, the founder of the University of Virginia.

Scientific achievement in the biological sciences was fostered immensely by the early scientific societies which developed in this country. Surgical progress was beginning to evolve in the early 19th century, and the influence of the great surgeons and universities in Edinburgh, London and later Germany and Austria was beginning to be felt in America. The rural nature of the new country with its vast area, poor roads and transportation, and lack of adequate communication discouraged the development of surgical organizations. On the other hand, these problems accentuated the need for surgeons to have personal contact with one another, to present to each other professional experiences, to exchange ideas, and to expound upon and discuss them. The minutes of one of the early meetings of the Southern Surgical Association record that a 20-min paper, presented at 2:00 p.m., evoked discussion which continued throughout the afternoon, and was begun again the next morning. This might be interpreted as an insatiable need for professional communication, and this need for communication and education was the primary stimulus for the establishment of most surgical organizations. Although originally intended for the education of fellow surgeons, the scope is expanded today to include an input into undergraduate, graduate and continuing education, not only of surgeons, but also nurses and allied health personnel. In addition, our surgical organizations have a great influence on the setting of educational standards and the makeup of certifying and qualifying bodies and examinations, and they often serve as advisors to the legislative and executive branches of government, and to government agencies on matters dealing with surgical health care legislation affecting education.

Another reason for these organizations was the desire for a forum to stimulate research. This reason was so well illustrated in the first Presidential Address, by Dr. W. D. Haggard, (Fig. 5) when, referring to the Southern Surgical Association, he stated,

> "It embraces a declaration of principles to which you may all unhesitatingly subscribe. Its face is set in the right direction, with its eyes fixed on the rising and not the setting sun. It forms a nucleus around which the votaries of science may gather, and as the great republic of letters form the democracy of science whose realms are penetrated by no royal road, but is open on all sides alike to those with persistent industry, energy and skill, shall ask to join the grand army of scientific observers. So we reach out our hands and invite into our circle such men as have by their works entitled them to the distinction of being educated, talented and industrious workers in the field of scientific research."[5]

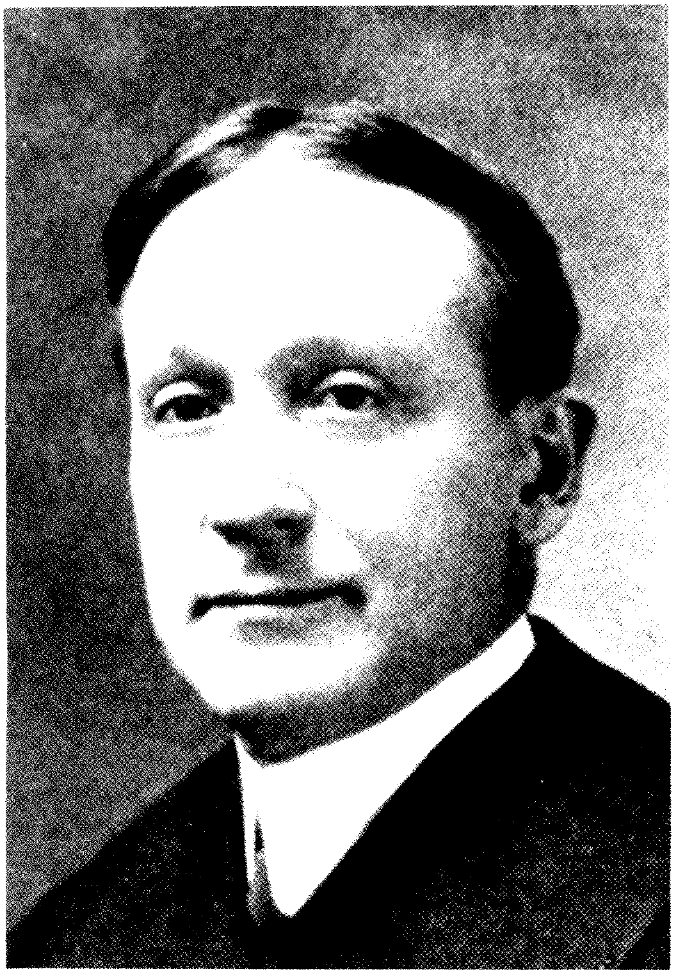


FIG. 5. The first President of the Southern Surgical Association, Dr. W. D. Haggard of Nashville, Tennessee (Courtesy of the American College of Surgeons).

That this is true today in this organization is demonstrated by the program you have before you at this meeting. The research influence is demonstrated even more vividly by the tremendous response and magnificent program of the Forum on Fundamental Surgical Problems of the American College of Surgeons, and the Forum of the Southeastern Surgical Congress, in addition to the programs of organizations devoted totally to surgical research.

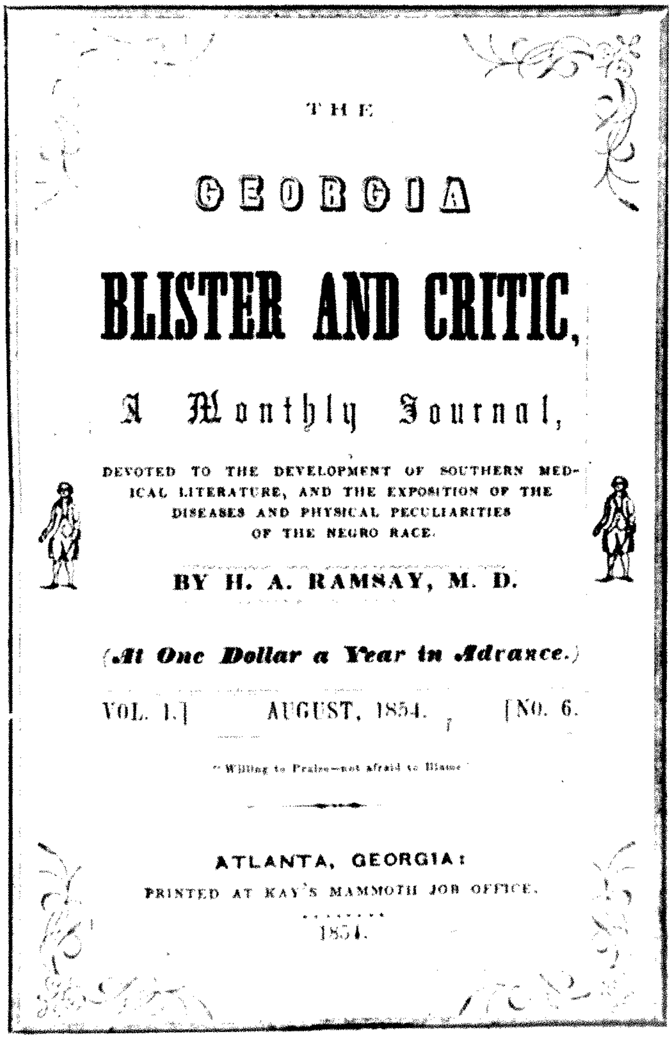
Organized surgery has always, and quite properly, involved itself vigorously in setting standards of quality for surgeons and facilities. However, before the advent of surgical organizations in this country, individual surgeons from time to time attempted to lay down their own standards of quality, and I am compelled to refer to the delightful address of Dr. Daniel Elkin (Fig. 6) before this organization in 1946, entitled *The Georgia Blister and Critic*. (Fig. 7) This is an account of one Dr. H. A. Ramsay of Raysville, Georgia, who published a medical journal under that descriptive name in Atlanta in 1854. The purpose of this journal was set forth as follows:

> "The high-toned and honorable in the profession will ever find this Journal the defender of their rights and privileges, while the empiric and knave, will be *blistered* as long as we can find a spot of cutaneous surface left to put one upon. With this programme, we presume our readers will understand our position, and govern themselves accordingly."[6]

Unfortunately, the writer of this noble admonition was ultimately convicted of fraud; he jumped bail and was never heard of again.

Today, virtually all of our societies have as a prime objective the elevation of standards of surgery and methods of improving and increasing the competence of surgeons, thereby improving the quality of patient care. A few relatively recent milestones in this endeavor are the establishment of surgical specialty boards and the Joint Commission on Accreditation of Hospitals, the latter initiated by the American College of Surgeons and established as a free-standing agency in the early 1950's. Moreover, the Residency Review Committtees, usually tripartite in structure and composed of representatives from the specialty boards, the American College of Surgeons and the American Medical Association, have had a tremendously favorable influence on the

FIG. 6. Daniel Collier Elkin (Courtesy of J. B. Lippincott Company, Philadelphia).



THE

GEORGIA

BLISTER AND CRITIC,

A Monthly Journal,

DEVOTED TO THE DEVELOPMENT OF SOUTHERN MEDICAL LITERATURE, AND THE EXPOSITION OF THE DISEASES AND PHYSICAL PECULIARITIES OF THE NEGRO RACE.

BY H. A. RAMSAY, M. D.

(At One Dollar a Year in Advance.)

VOL. I.] AUGUST, 1854. [NO. 6.

"Willing to Praise—not afraid to Blame"

ATLANTA, GEORGIA:
PRINTED AT KAY'S MAMMOTH JOB OFFICE.
1854.

FIG. 7. First page of the monthly journal published in 1854 by H. A. Ramsay, M.D., who was later convicted of fraud (Courtesy of J. B. Lippincott Company, Philadelphia).

quality of residency education and surgical care of patients.

The need for camaraderie and social exchange has been an important factor in the development of most surgical organizations, as is no better exemplified than in this one. Certainly, social activities provide an opportunity for intimate professional relationships and to know better distant professional colleagues as human beings, as well as to meet their spouses and families. Today, social exchange is a significant part of most surgical societies.

There are several other needs or objectives of organizations today which did not appear until relatively recently. Separatism between surgical specialties did not develop until the early twentieth century, and, therefore, liaison between specialty groups was not necessary. Today, however, cooperation among surgical and medical specialties is of the greatest importance, and organizations do, and must, play an increasingly significant part in maintaining effective communication.

Another vital need is for liaison with state and federal government agencies. This field of activity includes efforts as advisors for medical legislation, such as that enacted during the past decade, and continuing interest in pending legislation, where the opportunity often exists to counsel and testify on health-care related issues.

Finally, there is the need for data gathering and special comprehensive studies. Surgeons have always been data gatherers, especially where their own professional activities are concerned, and have from time to time studied special issues. About 5 years ago, it appeared that there was a compelling need for a comprehensive study of surgical services in this country, and the SOSSUS study was evolved initially by the American Surgical Association and the American College of Surgeons, but later included representation from regional and national specialty organizations. The chairman of the committee for this vast study, which was recently completed and published, is George Zuidema, a member of the Southern Surgical Association. The Association was ably represented on the committee by Valter Brindley.

So, we can see that there have been numerous reasons for the development of organizations, only a few of which are included here. They are not static reasons, but ever-changing and dynamic, fulfilling professional and societal requirements of the time.

Several organizations have had a particularly important influence on surgery in America and I wish to discuss briefly certain aspects of three of them. Two found their origins in professional journals and all three were born amidst opposition from individuals or other societies.

The first of these, and the oldest, is the American Surgical Association, founded in 1880 by a small group of prominent surgeons, led by Dr. Samuel Gross, (Fig. 8) who became the Association's first President. The formation was opposed by the American Medical Association on the grounds that the new organization would detract from the surgical section of that body. In his welcoming address at the second meeting in Philadelphia in 1882, Dr. Gross stated,

> "If it be said that we are striking a blow at the American Medical Association, we deny the soft impeachment. On the contrary, we shall strengthen that body by rousing it from its Rip Van Winkle slumbers, and infusing new life into it. We can hurt no society now in existence, or likely to come into existence. We can hurt only ourselves, if we fail to do our duty. We hope to make the American Surgical Association an altar upon which we may annually lay our contributions to Surgical Science and so show the world that we are earnest and zealous laborers in the interest of human progress and human suffering."[7]

At that meeting a constitution was adopted which stated that "the object of the association shall be the cultivation and improvement of the art and science of surgery, and the promotion of the interests not only of its fellows, but of the medical profession at large." This was later

FIG. 8. Samuel David Gross, first President of the American Surgical Association (Courtesy of J. B. Lippincott Company, Philadelphia).

changed so that the latter part now reads, ". . . and the elevation of the standards of the medical profession and such other matters as may come legitimately within its sphere." The constitution further stated, "To become a Fellow the candidate must have earned the reputation as a practitioner, or a teacher, or an original observer." Membership was restricted to 100 active Fellows and 25 honorary Fellows who were elected by ballot, and only three negative votes were required to cancel one's election. It is somewhat surprising that the organization flourished and prospered as well as it did in such a highly competitive and restricted atmosphere; however, by the third meeting, the limits for membership had been increased to 150 and, by the fifth, the secretary was directed to cast a ballot in favor of 50 candidates for active membership and 6 for honorary membership. International as well as national status was assured when, at the seventh meeting, the secretary read letters of thanks for the honor conferred by election to honorary fellowship from Professors Esmarck, von Langenbeck, Joseph Lister, Sir James Padgett, von Nussbaum, Zerney, Volkman, and Billroth. The rule allowing three members to prevent one's election to the Association was apparently too restrictive, because we find that, during the eighth meeting, the constitution was amended to require more than one-fifth of the votes be negative to deny a candidate admission.

Although the Association was apparently designed primarily as an honor society, a resolution was passed at its third annual meeting, instructing the President and Secretary to communicate with the United States Senate opposing reduction of the annual appropriation for the Museum and Library of the Surgeon General's Office from $10,000 to $5,000, a refreshingly small sum when compared to today's multimillion dollar appropriations. The importance of this library at that time cannot be overestimated, for it served as a national library of medicine. At the seventh meeting, an ambitious resolution was passed to organize a "Congress of American Physicians and Surgeons," which was to include nine associations representing both surgical and medical specialties and pathology. The proposer, Dr. C. H. Masden, stated that many men were members of several of these specialty societies, necessitating attendance at two or more meetings a year, with much loss of time to themselves and inconvenience to their patients, and also requiring a needless expenditure of money for these extra trips. An organization encompassing all of these specialty societies would allow these members to attend meetings of more than one association simultaneously, and eliminate these disadvantages. The Congress of American Physicians and Surgeons was subsequently formed and the first elected president was the eminent Dr. John Shaw Billings. It met at intervals of three years and was so structured that it would not interfere in any way with the autonomy of each specialty society. This

FIG. 9. Franklin H. Martin, founder of the journal Surgery, Gynecology & Obstetrics, and of the American College of Surgeons (Courtesy of the American College of Surgeons).

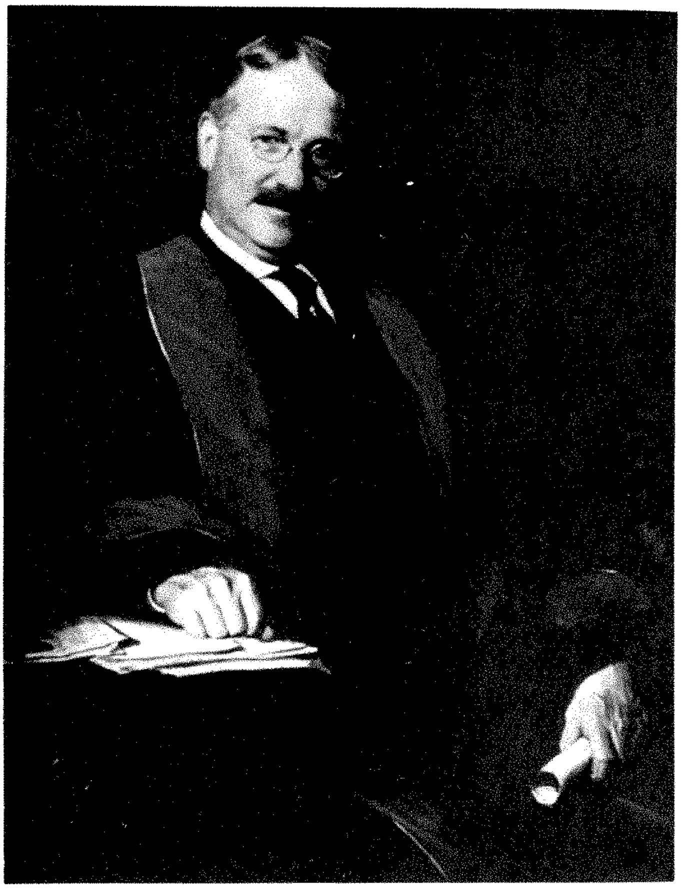


FIG. 10. John M. T. Finney, first President of the American College of Surgeons (Courtesy of the American College of Surgeons).

federation continued to meet for many years, well into the twentieth century.

In addition to evolving the American Board of Surgery and the SOSSUS study, the American Surgical Association had continued to excel in one of its primary purposes, that is, to serve as a forum where some of the finest scientific surgical work and clinical papers in this country are presented.

The American College of Surgeons is the largest surgical organization in this country and, indeed, the world, currently having in excess of 38,000 members, of which about 2,000 are from outside the United States, representing approximately 100 countries. The principal objectives at the beginning were "to elevate the standards of surgery and to establish a standard of competence and character for practitioners of surgery," objectives which are essentially unchanged today. Its history is well recorded by Loyal Davis in his interesting and informative book, *Fellowship of Surgeons.*[8] Founded in 1913, the American College of Surgeons can trace its origin to the surgical journal *Surgery, Gynecology & Obstetrics*. The journal was the brainchild of a Chicago gynecologist, Dr. Franklin Martin, (Fig. 9) who believed that there was a need for a different type of surgical journal, namely, one edited by surgeons for practical surgeons, and including articles in all of the special fields of surgery. He also believed that the profits should be used to strengthen the influence and worth of the journal rather than accrue to individuals or commercial publishing companies. Its success reinforced his belief that it was needed. Indeed it had been successful beyond his greatest expectations, and he began to consider other means to further the education of surgeons in America. The Society of Clinical Surgery had impressed upon him how much greater knowledge could be gained by actually witnessing operations in good clinics, as opposed to hearing or reading surgical papers. In 1910 his thoughts became focused toward inaugurating a clinical meeting whereby surgeons could visit Chicago clinics and observe operations from 8:00 a.m. 5:00 p.m. each day during a two-week period. Ten thousand invitations were issued, with an attendance of 200 expected. Instead, 1300 doctors appeared.

Over the ensuing two weeks Martin realized that while there were many surgical societies, there had never been a meeting like the one then in progress, and he observed that there was a strong movement to insure similar future meetings. A business session was held and the society was named The Clinical Congress of Surgeons of North America. The idea of an American College of Surgeons began to evolve and, over the next two years, Martin spent a great part of his time laying the ground work for such an organization by visiting groups of the most prominent surgeons in every major city in the country. Opposition and scepticism were great. The formation of the College was opposed by many surgeons, the American Medical Association and several state medical journals, most notably the *California State Medical Journal*. Its editor wrote sarcastic and demeaning editorials, both before and for several years after the College became a reality. This opposition, as well as Martin's cool reception by surgeons in San Francisco, were vividly depicted in the excellent Franklin Martin Memorial Lecture at the recent Clinical Congress by J. Englebert Dunphy.[9] After obtaining from the state of Illinois the incorporation papers for the American College of Surgeons, Martin attended the first meeting of its organizational committee on November 25, 1912, at Old Point Comfort, Virginia, where the Southern Surgical and Gynecological Association was holding its annual meeting. The reason for selecting this location was that a number of members of the organizing committee, including Charles Mayo, George Crile and J. M. T. Finney, were also members of the Southern Association, and Martin was himself an invited guest. Dr. Finney, the President of the Southern that year, was later chosen the first President of the new American College of Surgeons. (Fig. 10) A beloved member of this Association, he

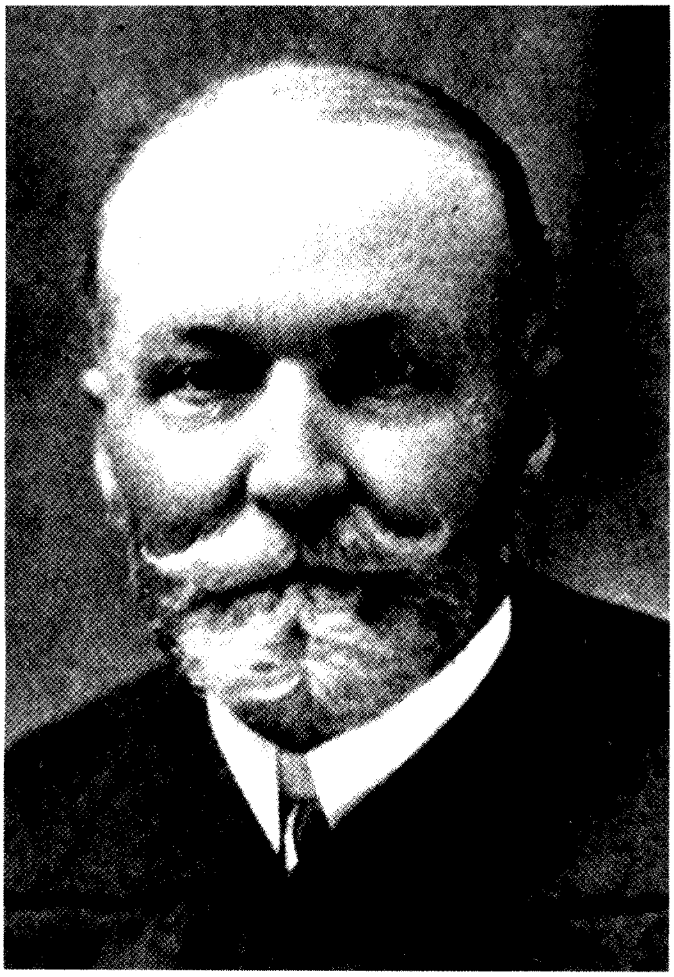


FIG. 11. John B. Murphy (Courtesy of the American College of Surgeons).

was the subject of Dr. Frank Wilson's Presidential Address in 1951. John B. Murphy, (Fig. 11) one of the leading surgeons of the day, and a prime mover in the organization of the College, had stated, "Finney is a simple man with direct courage and honesty. He has a sense of humor, which certainly helps the son of a minister." Davis points out that Finney was modest in his acceptance speech, and, as usual, forthright. He believed that the Association should be dedicated to the good of the country at large. He recognized the objections to its formation even in the minds of some in the audience. Finney confessed that he himself had had objections at first, but the more he had thought about the plan, the more firmly convinced he had become that it was needed. He urged the audience to unite and cooperate to eradicate the abuses which existed in the practice of surgery. Rudolph Matas, (Fig. 12) who was elected the first Vice-President and was a most eloquent speaker, stated,

> "I believe I am voicing the sentiments of my southern colleagues when I say that those of us who are here tonight are ready to support this movement with all our good will and best energies because we believe that this organization will be a powerful and beneficent agency in the uplift of the practice of surgery. We intend to cooperate with our fellows throughout the country, because we have confidence in an organization which has for its aim the elevation of the standards of American surgery not only to the level of the highest standards of the old world, but because it aims at the realization of the highest of our own American ideals of what the surgeon should be. It should be clearly understood that this movement is not calculated solely to benefit the surgeons themselves, but through the elevation of their own standards of efficiency and professional conduct, to benefit still more the suffering public at large"[10] (Figs. 13 and 14).

Although plagued with some growing pains initially and with some opposition, which included the development of a rival College, this College nevertheless flourished and its growth and influence since World War II have been unprecedented. In its effort to elevate and maintain the highest standards of surgery, the College has been constantly and vigorously opposed to such unethical practices as fee splitting, "ghost," "itinerant," and unnecessary surgery, surgical incompetence and a host of other improper practices.

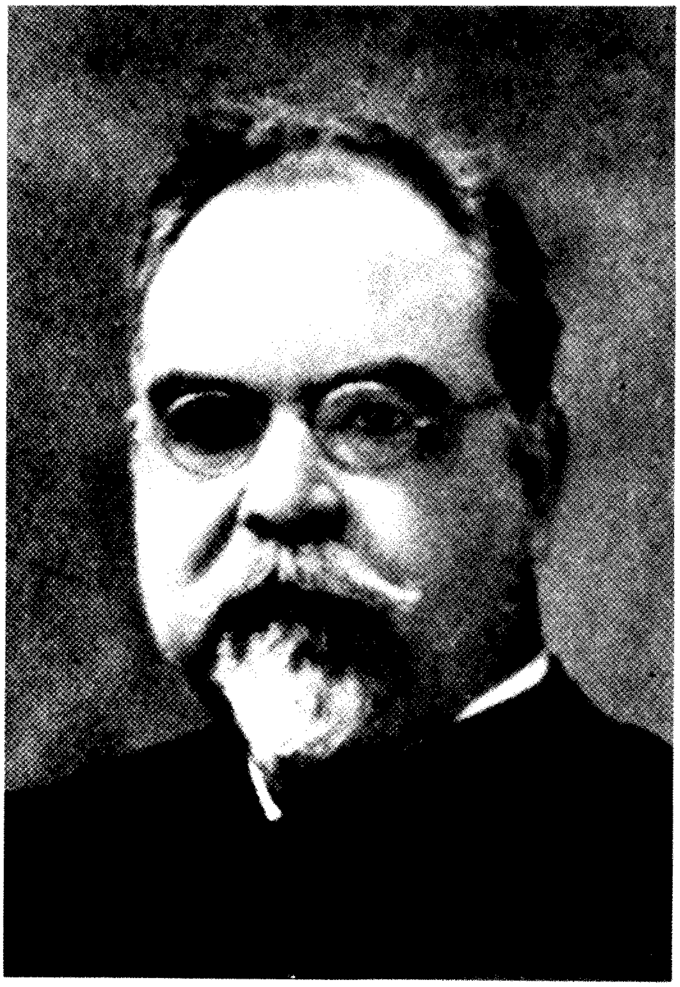
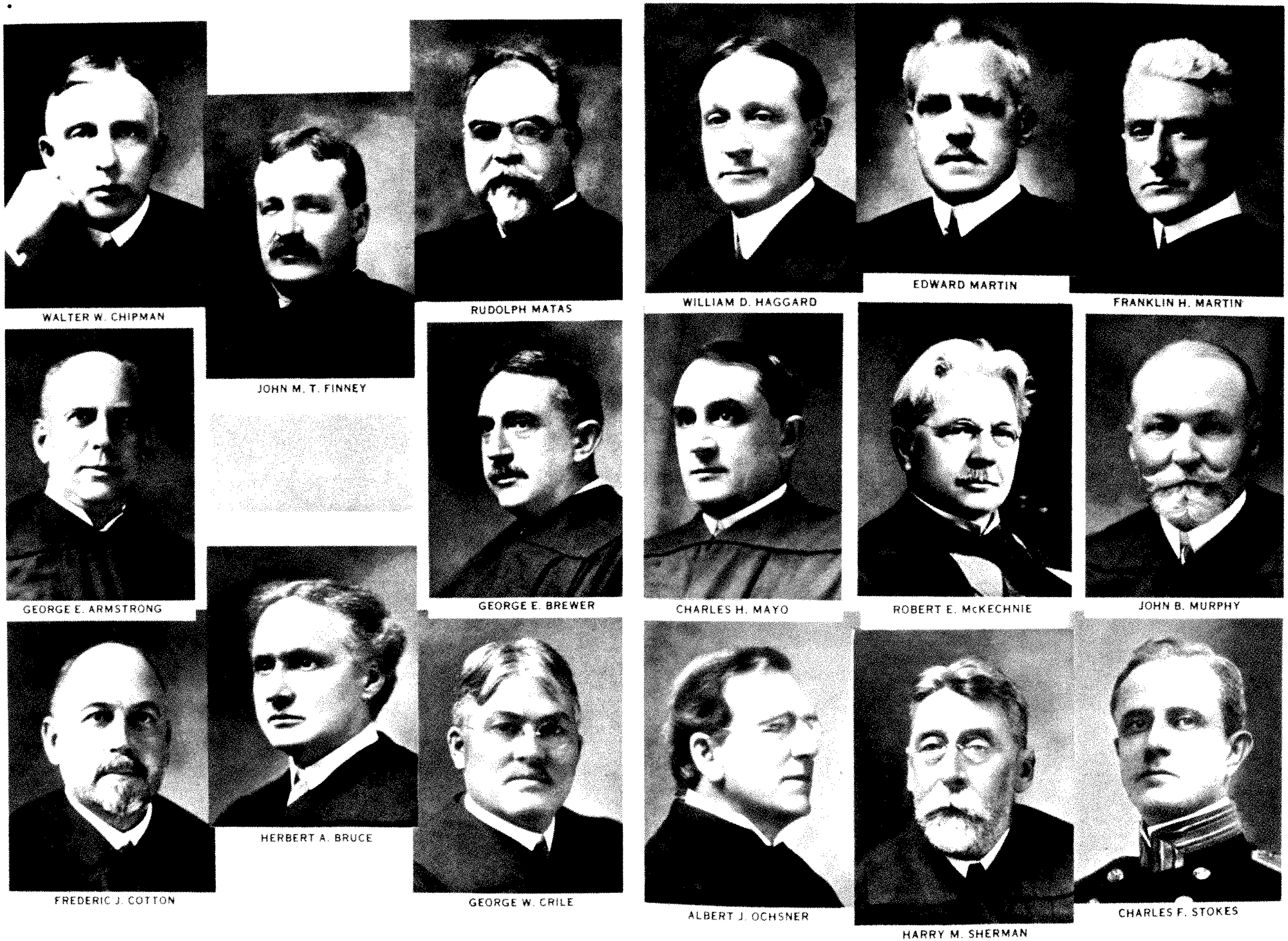


FIG. 12. Rudolph Matas, first Vice President of the American College of Surgeons (Courtesy of the American College of Surgeons).



WALTER W. CHIPMAN

JOHN M. T. FINNEY

RUDOLPH MATAS

WILLIAM D. HAGGARD

EDWARD MARTIN

FRANKLIN H. MARTIN

GEORGE E. ARMSTRONG

GEORGE E. BREWER

CHARLES H. MAYO

ROBERT E. McKECHNIE

JOHN B. MURPHY

FREDERIC J. COTTON

HERBERT A. BRUCE

GEORGE W. CRILE

ALBERT J. OCHSNER

HARRY M. SHERMAN

CHARLES F. STOKES

FIG. 13. Members of the original Board of Regents, American College of Surgeons, 1913 (Courtesy of the American College of Surgeons).

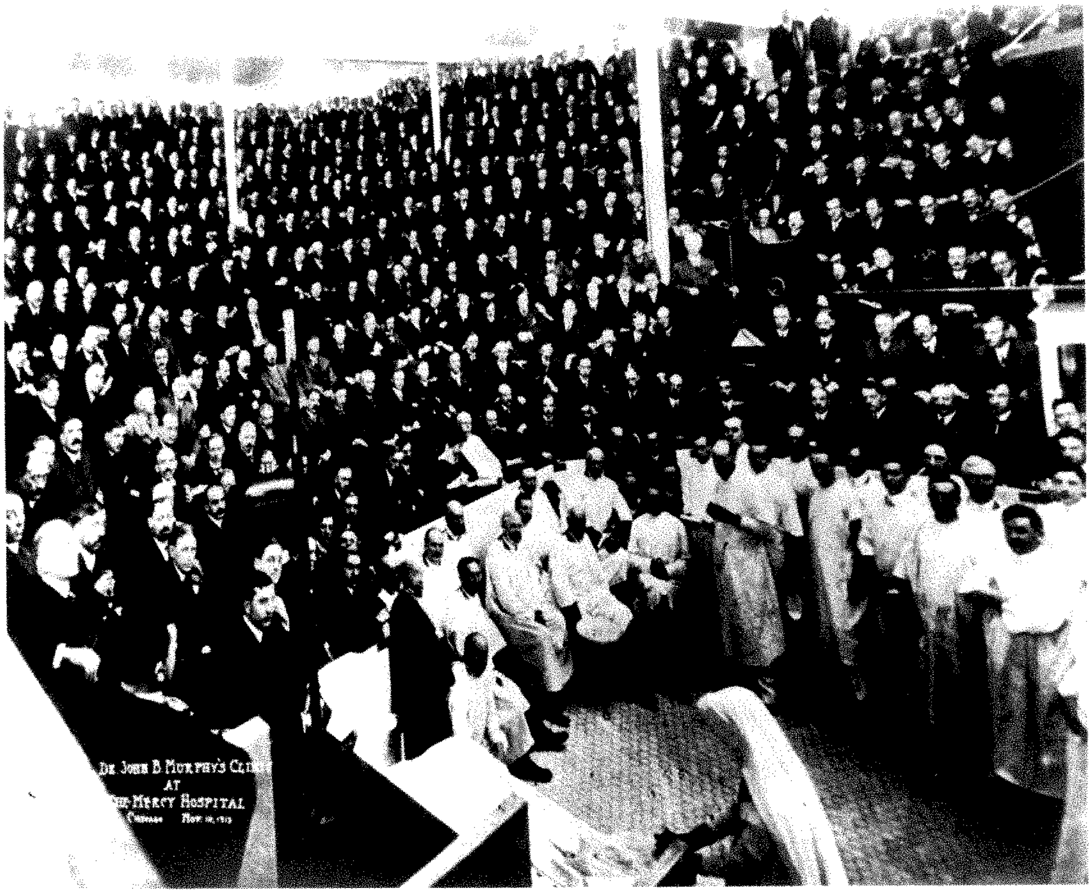

Dr. John B Murphy's Cl
AT
Mercy Hospital

FIG. 14. John B. Murphy's operating clinic during the 1913 meeting of the Clinical Congress of Surgeons (Courtesy of the American College of Surgeons).

One of the primary aims of the College is the continuing education of surgical practitioners, and its annual Clinical Congress provides the greatest variety of excellent educational programs to be found anywhere. The recently instituted spring meetings provide in-depth postgraduate courses on selected subjects of general and special interest. The self-education and assessment examination, or SESAP as it is called, is in its second edition, and has been a most successful modality to reveal individual deficits of knowledge while at the same time providing education in these areas. A newly formed Department of Education within the College should serve to strengthen and expand its educational efforts.

The College has exerted an especially salutary influence in bringing together, supporting, and encouraging the various surgical specialties to the extent that they now comprise more than 50% of its membership. This serves to strengthen the broad field of surgery, to encourage educational exchange and to reveal problems or issues which might be peculiar to one or more of the specialties.

Although it is not an official lobbying organization, the American College of Surgeons nevertheless maintains an excellent liaison with government organizations and contributes significant input in terms of testimony before congressional committees and direct communication with governmental agencies.

The structure of the College allows great versatility, responsiveness, expert consideration of problems and the ability to take action on important issues. The director and the assistant directors are skilled surgeons and able administrators, and, combined with a large and dedicated staff, they provide the framework and central nucleus to effect the College's policies and activities. In addition to the officers and the highly representative governing body, the state chapters contribute immeasurably to its overall strength. No other surgical organization has its structure, strength and potential, and my personal feeling about the American College of Surgeons was expressed admirably by the immediate past president, Charles McLaughlin, when he said, "It has contributed more to the high standards of surgical practice, to surgical education, and to improvement in the care of the surgical patient, than any other organization in the western hemisphere."[11] It is of interest that the last five presidents of the College, including the current one, H. William Scott, are members of the Southern Surgical Association.

The offices of the College formerly occupied a stately house, the Nickerson residence, (Fig. 15) but in 1964 they became housed in a handsome, new, much more efficient building, paid for by the Fellowship and located across the street at 55 East Erie. (Fig. 16)

Finally, one of the greatest of these organizations, the

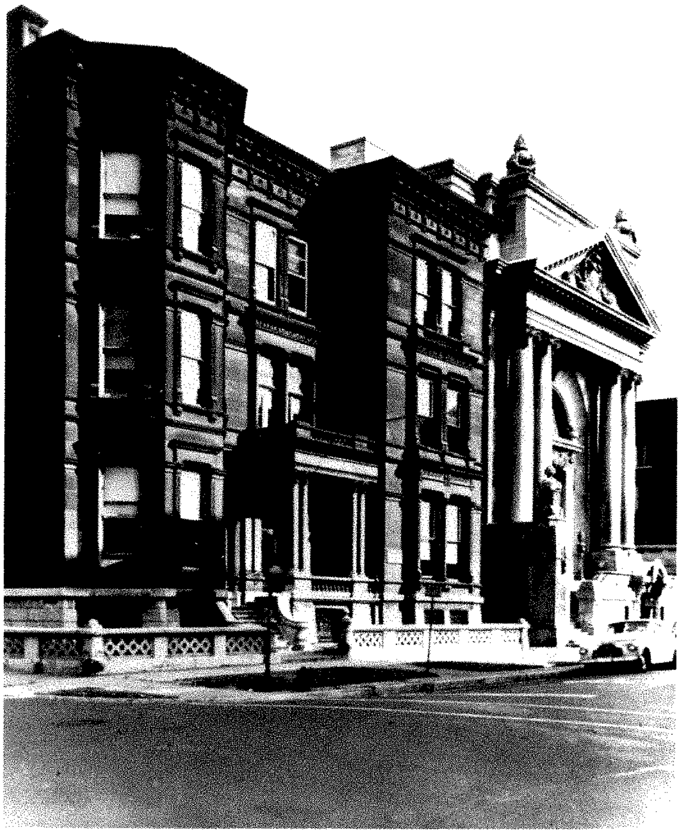


FIG. 15. Nickerson Residence, which served as headquarters for the American College of Surgeons until 1964 (Courtesy of the American College of Surgeons).

Southern Surgical Association, is not the oldest, and not the largest, but, in addition to exerting a profound influence on the profession, is, I believe, the organization which calls forth the greatest affection and devotion from its members of any of which I know, or with which I have been associated. It originated through the genius of the Davis brothers (Figs. 17 and 18) of Birmingham, Alabama, and was born both because of needs which have already been stated, and out of political expedience. Its history is beautifully recorded by Dr. Robert Moore.[12] Like the ACS, its origin can be traced to a surgical journal. The Davis brothers began to publish the *Alabama Medical and Surgical Journal* in 1886, and in that same year, a small group of surgeons gathered in its office to establish the Alabama Surgical and Gynecological Association. The younger Davis, then only 23, was Secretary of the Alabama Association and was opposed to a Southern Association, believing that too few men from each state would be qualified, but that state organizations could in time develop more distinguished members who would be elected to a more exclusive Southern Association. The younger Davis went to Europe for 6 months, leaving his brother to edit the Journal, but the journal's demise was signalled by financial difficulties, the elder Davis's very busy practice and, more important, the loss of a battle with regard to medical licensure in Alabama to Dr. Jerome Cochran, a powerful political figure who had organized the state medical association. It is noteworthy that this editorial battle arose because the Davis brothers had argued vehemently for a single state Board, which would examine only medical graduates for licensure. Cochran, on the other hand, favored continuing the county examining boards, which examined candidates who were not necessarily medical graduates. Thus, one of the first issues in the establishment of the Southern Surgical Association had to do with elevation of medical and surgical standards. When the younger Davis returned from Europe, he found that not only had the publication of the Journal been suspended, but that Cochran had become very apprehensive about the competition which the new organization might give the state medical society. Because of his political strength and a campaign which he vigorously waged, prospective members, as well as many of those who had attended the initial meeting of the Alabama Association, lost enthusiasm. The Davis brothers ignored the old adage, "If you can't lick 'em, join 'em," and immediately wrote letters to many surgeons in the southern states, soliciting support of a southern surgical organization. Favorable responses from

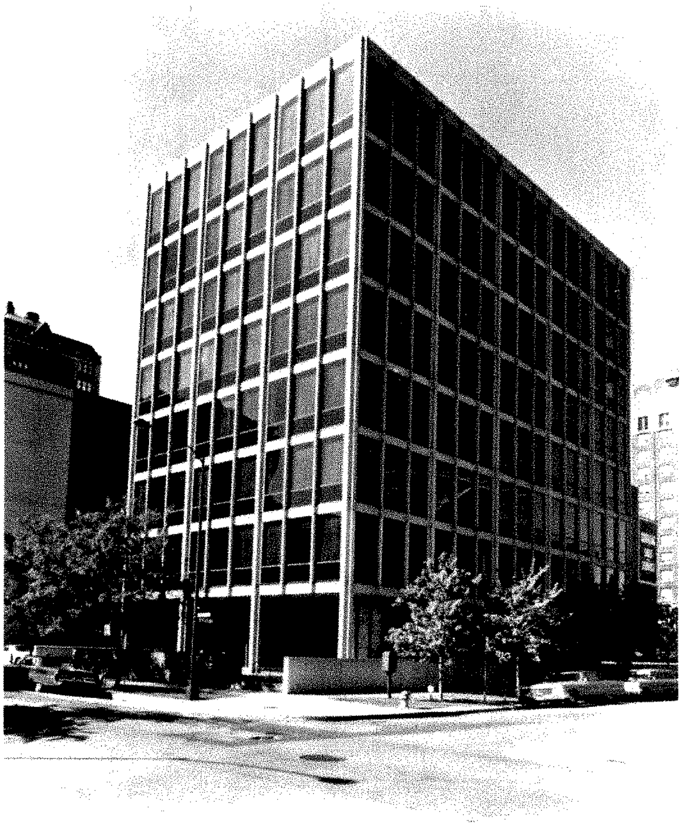


FIG. 16. The current headquarters of the American College of Surgeons (Courtesy of the American College of Surgeons).

FIG. 17. John Daniel Sinkler Davis (Courtesy of J. B. Lippincott Company, Philadelphia).

80 surgeons launched the first meeting on October 12, 1887, and Dr. W. D. Haggard of Nashville, who had been one of the most enthusiastic respondents, was elected President of the new Southern Surgical and Gynecological Association. It was recommended by the Council that membership not be limited to a specific number, but that the standard of requirements for membership be so high that only the best surgeons would be eligible. Throughout its early development, education and research were emphasized and, indeed, Article 2 of the original constitution states, "The object of the Association shall be to organize the profession in the South in the most efficient manner possible for the advancement of the sciences of surgery and gynecology." Candidates for membership were required to submit with their applications a paper on a surgical or gynecological subject, and new members were expected to present papers at the first meeting following their election. In addition, Article 8 of the By-Laws required the President to appoint 15 members, each of whom was to prepare and read an essay or lecture on some subject of his own selection. Initially, it was customary for the membership to be subjected not only to a Presidential Address, but also to an annual oration by one of the members. The first annual orator, Dr. W. F. Hyer of Mississippi, expressed the object of the Association to the membership as follows:

> "The true physician is always diligent in search for knowledge. He utilizes every means at hand for its attainment. He burns the midnight oil. He attends associations where he may meet with his brethren, and brightens his intellect, and sharpens his faculties by the friction of mind against mind, while discussing subjects of interest to the profession. For this object, the Southern Surgical and Gynecological Association was organized; for this purpose we are assembled in Birmingham today. The southern physician in every state has his association, with which he may affiliate, but there has for a long time been recognized the need of an association for the advancement especially of the branches of medical science known as surgery and gynecology. These associations are common in the more thickly settled northern states, but in the South, we have felt their needs."[13]

He ends his oration by stating, "May its career be prosperous, and tend at all times to lift the profession in the South to a higher plane of usefulness."

The Association has always been a unique organization; first of all, it is not regional, as the name implies, but, as reiterated in the excellent address last year by David Sabiston,[14] the membership is drawn from throughout the United States, and the association from its beginning "opened wide its doors with a hearty welcome to

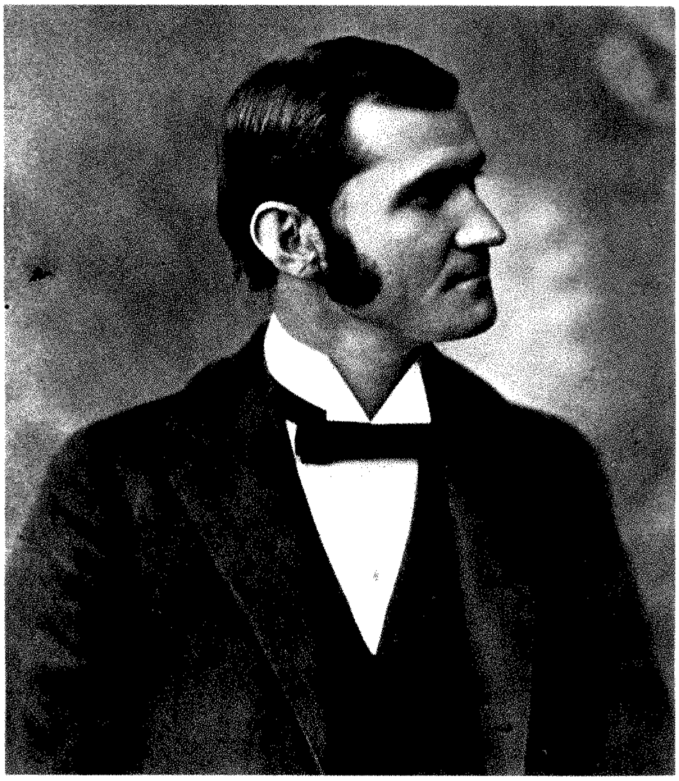


FIG. 18. William Elias Brownlee Davis (Courtesy of J. B. Lippincott Company, Philadelphia).

distinguished men of ability from all sections of our common country." In a splendid fashion, it has combined the objectives of the advancement of the science of surgery and encouragement of investigation with a certain social tenor which has made it the envy of many other organizations.

Initially, it was customary to be welcomed by the mayor of the city in which the meeting was held, the most noteworthy such occasion being the welcome in 1903 by the mayor of Atlanta, who said, "If there is anything in this city that you would care to have, it matters not what it is, you are welcome to it. There are no keys to the city of Atlanta. Mr. Sherman took the keys some years ago and forgot to return them." In 1893, in New Orleans, the members were guests at the Pickwick and Boston Clubs during their stay, and the managers of the French Opera presented "Faust" in honor of the occasion. Guests today are welcomed to the annual banquet, and this is the only organization of its type that I know of which encourages the families and guests of members to attend the final business meeting. Thus, in addition to scientific surgical endeavor, so well exemplified in the program you are about to hear and in which you are about to participate during this meeting, a feeling of warmth, friendship and camaraderie prevails throughout.

This Association means different things to different members. Dr. George Ben Johnston expressed his feelings to the Association in 1897, when he said,

> "I have not mistaken your motive in choosing me as your President. I am aware that you did not intend to exalt the individual, but to reward a faithful member whose heart is in this Association, and whose highest privilege is to style himself a member."[15]

Dr. Frank Johns repeated this statement 50 years later as representing what the Association meant to him, and I also subscribe to this sentiment. I must also mention Dr. Francis Massey, the subject of whose Presidential Address was "What the Southern Surgical Association Means to Me." He stated,

> "What I am about to say to you has not been said on like occasions. Perhaps because it is not considered in good taste to express in public words of affection and respect for one's mother; but I remind you I am speaking to younger brothers, sons of our same mother, the Southern Surgical Association."[16]

He states further,

> "These meetings are not trivial. They are gracious interludes in a schedule of hard work; they are sweet relief from constant responsibility. . . . Even the medieval monks in their severe ascetic monasticism realized the healing qualities of rest and relaxation after long and tiresome tasks. At the end of transcribing in Latin seemingly endless manuscripts . . . they often would add, 'NUNC scripsi totum. PRO CHRISTO da mihi potum.' For those of you no more familiar with Latin than I, the translation, in all sincerity, and with no thought of irreverence, is 'Now I have finished writing the whole thing. For Christ's sake give me a drink.' "[17]

And so, surgical organizations have had and continue to have most enlightening and beneficial influences on surgeons and surgery. They stimulate the intellect, provide a forum for the exchange of ideas and experiences and the presentation of original studies. They set the standards for surgical education and practice and improve the quality of patient care.

The Southern Surgical Association embodies many of these influences so well. I believe that a portion of the statement by Alan Gregg, referring to the Johns Hopkins Medical School and Hospital on the centenary of the birth of William H. Welch, may be aptly applied to this Association. He said,

> "I suggest that something extraordinarily precious comes out of the close but entirely free association of really superior people. To this emergent quality I give the name—the heritage of excellence, mostly because . . . it never comes from nor appeals to mediocrities. What more do men of superior character and capacity require for their association than freedom, responsibility and expectation."[18]

Undoubtedly, all of us in the Southern Surgical Association feel strongly this heritage of excellence.

Election to membership is an achievement which we all treasure. To be your President is a humbling privilege, an honor, and indeed a delight which has no equal and for which I am most grateful.

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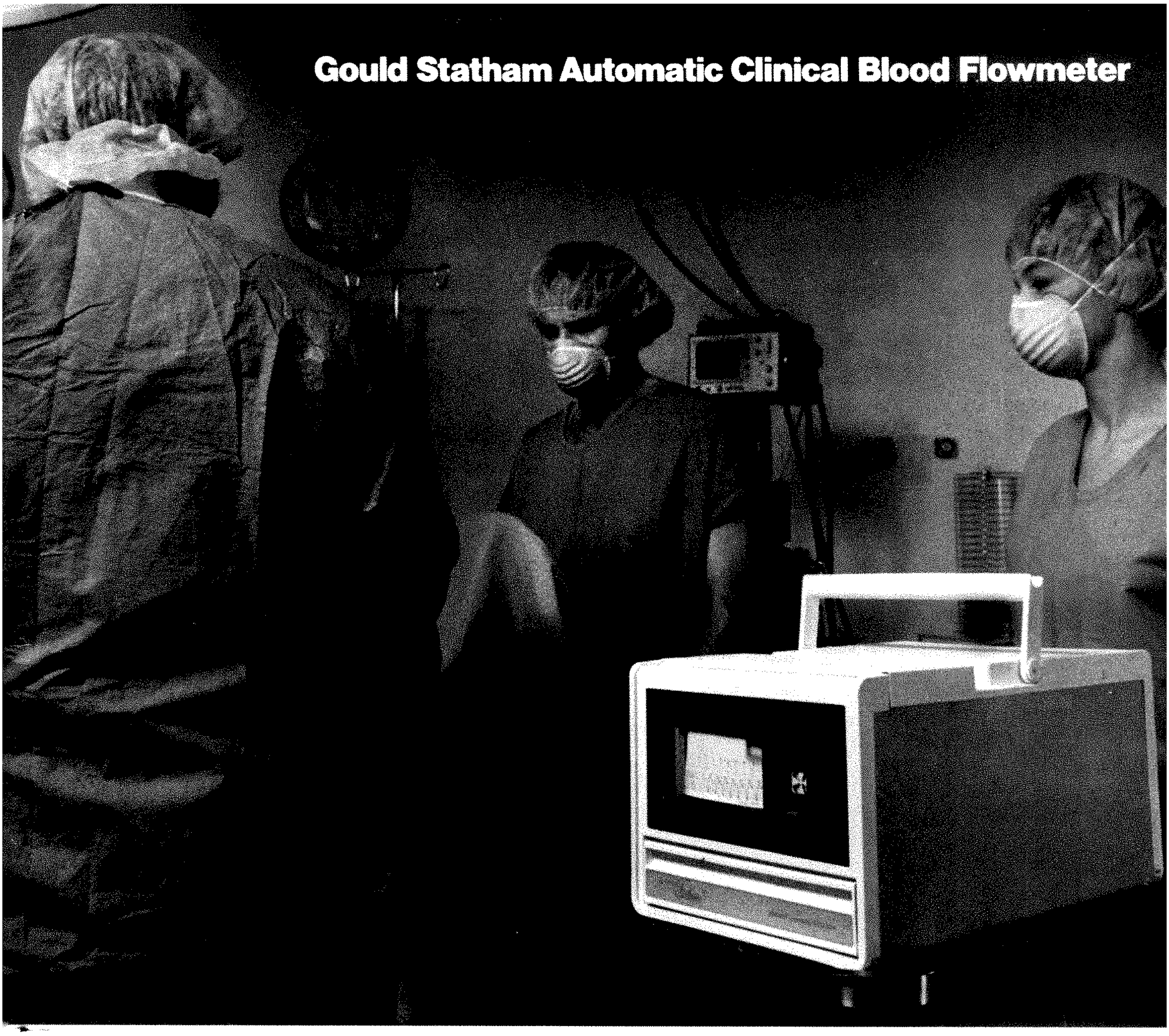

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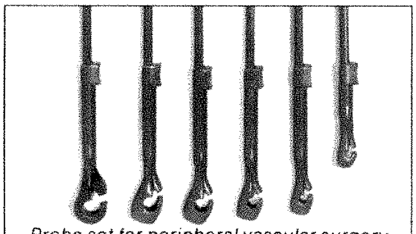
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a valuable adjunct during the various phases of cancer management

CEA-ROCHE has been the subject of numerous clinical studies over the past four years to assess its value in cancer management. Most investigators have found this assay to be a useful biological marker for following the clinical course of patients with many types of internal carcinoma.* These studies have reported CEA-ROCHE to be a valuable adjunct in the overall evaluation of the patient's clinical progress and prognosis by indicating...

- lack of response to or escape from therapy
- need for a change or reevaluation of therapy
- development of metastases and/or local recurrence
- the need for more intensive patient examination and observation since a rise in CEA titer has been reported to precede other evidence of recurrence by periods averaging 2 months and up to as much as 29 months.*

CEA-ROCHE may also be used...

- as an adjunct to other diagnostic tests or procedures in the patient suspected of having cancer

*Literature available upon request from Professional Services Department, Roche Laboratories, 340 Kingsland Street, Nutley, N.J. 07110.

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CEA-ROCHE
Carcinoembryonic Antigen assay

Suggested Guidelines for the Use of CEA-ROCHE as an Aid in the Management of the Cancer Patient*

Type of Therapy	When to order CEA-ROCHE	Why order CEA-ROCHE
	During Periods of Active Therapy	
Surgery	As part of the presurgical workup and approximately 3 weeks after surgery	To monitor the effects of surgery[1-4]
Radiotherapy	Prior to initiating radiotherapy, once at midpoint and/or upon completion of radiation	To monitor the effects of radiation[1,2,5,6]
Chemotherapy	Prior to initiating chemotherapy, once at midpoint if therapy extends over a 6-week period and upon completion of chemotherapy	To monitor the effects of chemotherapy[1,2,5,7]
	During Short-term Follow-up After Therapy	
All types	Every 1 to 2 months during the first 6 months following therapy	To provide a basis for the reevaluation of therapy and/or an early indication of recurrence or progression of disease[1,2,8]
	During Long-term Follow-up	
All types	Every 6 to 12 months	To provide an early indication of recurrence or progression of disease[1,4,9,10]
	During Active Change in Clinical Condition	
All types	Every two weeks until trend is established	To aid in determining the probable presence of metastases or local recurrence[1,2,4,10]

When using this assay remember CEA-ROCHE is…

- *not* specific for any one type of cancer
- best used *periodically* to establish a trend, usually identifiable within 30 to 90 days
- *not* an absolute test for malignancy and should not be used as the sole criteria for diagnosis (use with other diagnostic tests and procedures)
- *not* recommended as a screen to detect cancer

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*These are general guidelines for the use of CEA-ROCHE only and may vary widely depending on such factors as patient status, clinical symptoms, type of malignancy, results of other tests and procedures.

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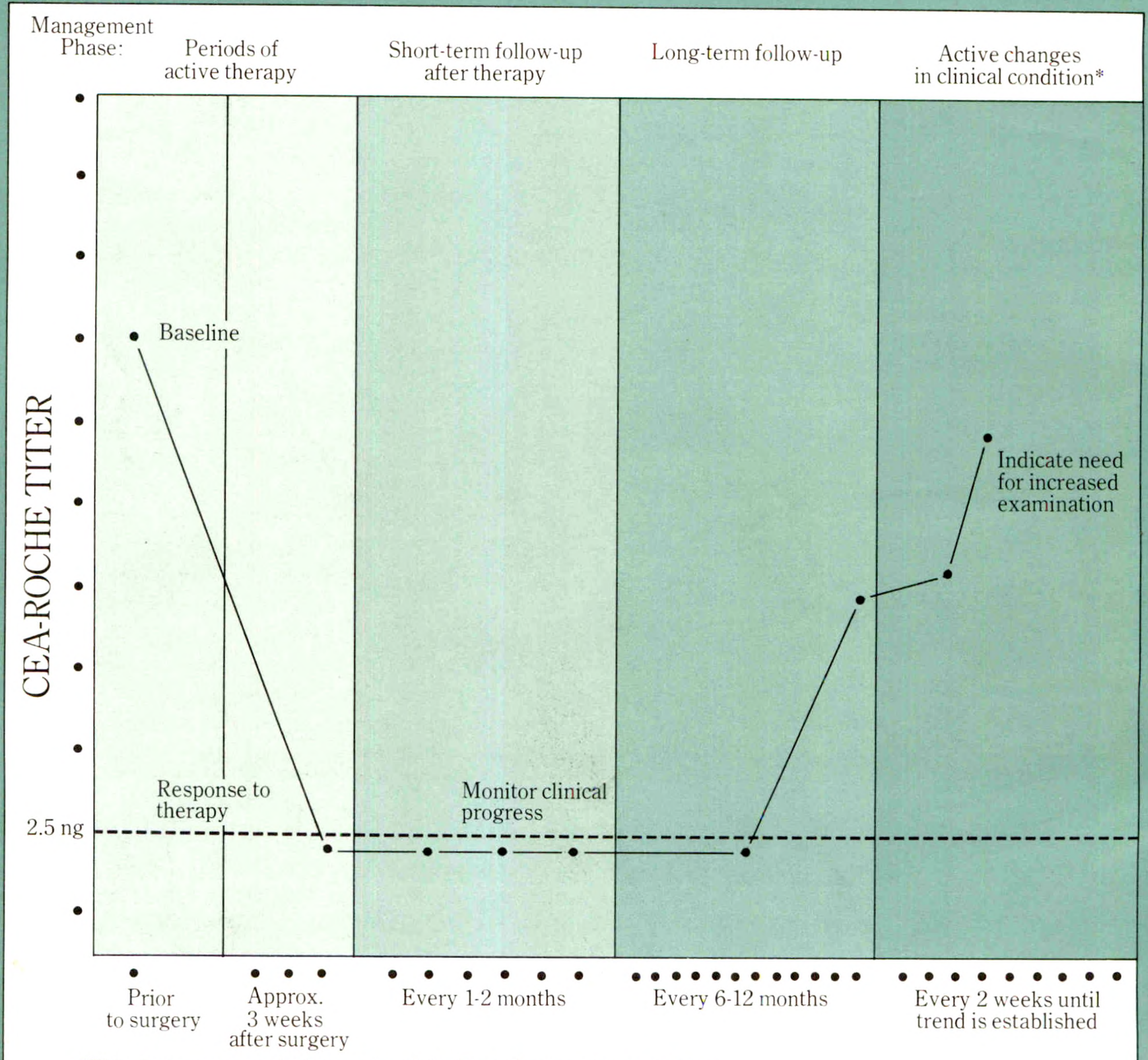
ROCHE

When to use CEA-ROCHE as an aid in the postsurgical management of a cancer patient

A simulation of a representative patient showing graphically when to perform CEA-ROCHE assays using the suggested guidelines appearing on the reverse side.



*This phase may occur during any one of the three other management phases.

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Additional information may be obtained from
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  (201) 235-4873

Evaluation of Dominant Thyroid Masses

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Controversy exists concerning the management of solitary thyroid nodules because of conflicting information concerning the high clinical incidence of thyroid nodules, the varying incidence of cancer reported in those surgically excised and the infrequency of death from thyroid cancer. During the past several years, a plan for evaluating patients with dominant thyroid masses has evolved. The objective is to avoid unnecessary operations by identifying patients with a high risk of cancer. The criteria which are used are the age and sex of the patient, the duration of the mass, ^{125}I or ^{99m}Tc scans, ^{75}Selenomethionine scans, B-mode ultrasonography and the response of the mass to suppressive therapy. This is a report of the findings in 222 patients who have been studied employing this approach. Thirty per cent of the patients were operated upon. Forty per cent had neoplasms (well differentiated cancer—28.8%, adenoma—12.1%), 47.0%—nodular goiter, 6.1% cysts, and 6.1% chronic thyroiditis. The incidence of cancer in the 222 patients was 8.6% and adenoma 3.6%. Patients at greatest risk of having cancer are those with solid nonfunctioning nodules which fail to regress with suppressive therapy. This study indicates that the approach described above is effective in selecting for surgical excision those individuals at greatest risk of having thyroid cancer.

THE MANAGEMENT of thyroid nodules is controversial. This is because of conflicting information concerning the incidence of thyroid cancer in surgical specimens, at autopsy and the infrequency of death from this disease.[12,24,26] It is a common clinical problem because of the high clinical incidence of nodular goiter from which thyroid cancer needs to be differentiated.

Thyroid cancer was regarded as a curiosity of little clinical significance until attention was called to its high incidence in patients operated upon for nontoxic nodular goiter by Cole *et al.* in 1945.[8] Subsequent reports from many parts of the world have indicated the incidence of thyroid cancer in patients with thyromegaly to be highly variable. It has been reported in from 5 to 38% in surgical specimens.[12,15,18,21,25] Demographic factors do not completely explain these discrepant figures.[16] Differing criteria for selection of patients for operation is a more important factor.

There is fairly good concensus concerning the management of a patient with a thyroid nodule which is probably carcinoma. More challenging is the evaluation and appropriate treatment of the patient with an asymptomatic solitary nodule or dominant mass in the thyroid which probably is not cancer. The extremes of management vary from suppressive therapy of all nodules to their surgical removal. Since physical findings of benign and malignant thyroid disorders are not distinctive, a variety of criteria have emerged which are used in an effort to distinguish between them. One of the earlier and more useful methods is to determine the functional status of a nodule or dominant mass as measured by its ability to concentrate radioiodide. There are, however, distinct limitations of the ability of scans to appraise accurately the intrinsic radionuclide content of a thyroid nodule. Therefore, scans have been considered by some to be of little discriminating value.[19,22] Other methods which have been developed to differentiate between benign and malignant nodules include scanning with ^{75}Selenomethionine,[27] B-mode ultrasonography,[1,23] thermography,[7] needle biopsy,[10,11,29] a trial of suppressive therapy,[3,12,17] and serum human thyroglobulin levels.[28]

During the past several years we have developed a decision matrix, for evaluating patients with a dominant thyroid mass. The objective was to provide an alternative to excision of all thyroid nodules. This study was designed to determine the effectiveness of this approach in selecting patients for operation with the highest risk of thyroid cancer.

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TABLE 1. *Sex and Age of 222 Patients With Solitary Nodules (Dominant Masses) in the Thyroid Gland With a Clinical Diagnosis (No Operation) and a Pathological Diagnosis (Based on an Open Operation)*

			Sex				Age			
			Female		Male		<41		>40	
	#	%	#	%	#	%	#	%	#	%
Clinical Diagnosis										
Cyst	8	5.1	8	100.0	0	00.0	4	50.0	4	50.0
Thyroiditis	8	5.1	7	87.5	1	12.5	5	62.5	3	37.5
Nodular Goiter	140	89.7	122	87.1	18	12.9	69	49.3	71	50.7
Total	156	100.0	137	87.8	19	12.2	78	50.0	78	50.0
Pathological Diagnosis										
Cyst	4	6.1	3	75.0	1	25.0	2	50.0	2	50.0
Thyroiditis	4	6.1	4	100.0	0	00.0	1	25.0	3	75.0
Nodular Goiter	31	47.0	27	87.1	4	12.9	12	38.7	19	61.3
Adenoma	8	12.1	8	100.0	0	00.0	8	100.0	0	00.0
Cancer	19	28.8	14	73.7	5	26.3	8	42.1	11	57.9
Total	66	100.0	56	84.8	10	15.2	31	47.0	35	53.0

Materials and Methods

Admission of patients to the study was based upon a request for a thyroid scan to evaluate an asymmetrical enlargement of the thyroid gland. Two hundred and twenty-two patients seen from January 1, 1971 through March 1, 1975 provided the material for the study. On the basis of the clinical findings, all lesions were categorized as solitary nodules (dominant masses), multinodular or diffuse goiters. All the thyroid scans were carried out using ^{125}I or ^{99m}Tc and interpreted by one of us (ES). Scans were made with a 3″ × 2″ NaI (TL) detector (Picker Magnascanner). For ^{99m}Tc thyroid studies the procedure was to use a scan speed of 60 cm/min for a thyroid count rate in the range of 20,000 to 50,000 cpm and a scan speed of 120 cm/min for a thyroid count rate of 50,000 to 100,000 cpm. ^{125}I thyroid scans typically had a count rate over the thyroid on the order of 2,000 cpm and a scan speed of 30 cm/min was used. In all cases the step size was 0.15 cm and a low energy collimator with 73 holes, 3″ focal depth was used.

Most patients with hyperfunctioning nodules were excluded from further evaluation. Patients with thyroiditis were also excluded except for those who were operated upon because of a high index of suspicion of cancer. Patients who proved to have a multinodular goiter were also excluded unless there was a dominant mass or nodule. Non, hypo, or normally functioning nodules were further appraised by B-mode ultrasonography. A Unirad Sonograph I diagnostic recorder with a 2.25 mega hertz transducer was used. The results were recorded on Polaroid film from an oscilloscope screen. Solid and cystic masses were differentiated. The latter were categorized as being either pure or mixed with a solid component. Pure cystic lesions were managed by aspiration with histological examination of the aspirate. These patients were followed unless there was a residual mass or immediate recurrence of the cyst. Hypo or normally functioning solid lesions, presumed to be a manifestation of a nodular goiter because of some uptake of radionuclide,[13] were managed by suppressive therapy for a minimum of 6 months. This therapy consisted of: A) 75 to 100 mcg of triiodothyronine daily with monitoring of TSH suppression by the fall in the serum thyroxine to hypothyroid levels, or B) 0.2.–0.3 mg of thyroxine with monitoring by measuring serum TSH levels. Individuals having complete regression of their nodules were followed. When there was no or incomplete regression surgical excision was advised.

Nonfunctioning solid lesions were further evaluated by ^{75}Selenomethionine scanning. When there was selective concentration surgical excision of the lesion was advised. When there was no selective concentration of this isotope suppressive therapy was commenced as outlined above. Needle biopsy was done in selected patients to confirm the clinical diagnosis of thyroiditis or in patients with a dominant nodule in whom a trial of suppressive therapy was considered inadvisable because of age or other factors indicating poor risk or limited life expectancy.

The differences between groups of patients were examined for statistical significance using Student t test and Chi Square method. Only those differences which were found to be significant are indicated.

In Table 1 are recorded diagnoses, sex and age of the 222 patients providing the clinical material for this investigation. The basis for inclusion in the study was the presence of a dominant mass detected on physical examination of the thyroid gland. The clinical diagnoses were made on the basis of the history, physical findings, radionuclide scans, ultrasonography and the response to suppressive therapy. The clinical diagnosis group of patients with thyroiditis includes 4 in whom the diagnosis was confirmed by needle biopsy. The pathologic diagnoses

TABLE 2. *Interpretation of ^{125}I-^{99m}Tc Scans of 222 Patients With Solitary Nodules (Dominant Masses) in the Thyroid Gland With a Clinical Diagnosis (No Operation) and a Pathological Diagnosis (Operation)*

		No Function		Hypo-function		Normal		Hyper-function		Other	
	#	#	%	#	%	#	%	#	%	#	%
Clinical Diagnosis											
Cyst	8	5	62.5	3	37.5	0	00.0	0	00.0	0	00.0
Thyroiditis	8	1	12.5	1	12.5	0	00.0	0	00.0	6	75.0
Nodular Goiter	140	11	7.9	39	27.9	26	18.6	21	15.0	43	30.7
Total	156	17	10.9	43	27.6	26	16.6	21	13.5	49	31.4
Pathological Diagnosis											
Cyst	4	0	00.0	2	50.0	2	50.0	0	00.0	0	00.0
Thyroiditis	4	1	25.0	1	25.0	0	00.0	2	50.0	0	00.0
Nodular Goiter	31	2	6.5	13	41.9	1	3.2	5	16.1	10	32.3
Adenoma	8	4	50.0	3	37.5	0	00.0	1	12.5	0	00.0
Cancer	19	9	47.4	7	36.8	1	5.3	1	5.3	1	5.3
Total	66	16	24.2	26	39.4	4	6.1	9	13.6	11	16.7

were based upon histologic study of thyroid tissue removed at the time of an *open* operation. The pertinent findings are: 1) 29.7% of the patients were operated upon to identify or exclude thyroid cancer. 2) 18.1% of patients with nodular goiter (clinical plus pathological diagnosis) were operated upon. 3) 28.8% of patients undergoing thyroidectomy for diagnosis had carcinoma and 12.0% had adenomas. All of the cancers proved to be well differentiated. 4) Cysts, thyroiditis, nodular goiter and carcinoma of the thyroid occurred 7.5 times as often in women as in men. The relatively high incidence of cysts and adenomas in women is of interest but not of statistical significance. 5) Nodular goiter and carcinoma were more common above 41 years of age. However, this association to ageing was not striking or statistically significant. Of interest is the observation that all patients with adenomas were younger than 41 years at the time of operation.

The data obtained by radionuclide scanning with ^{125}I or ^{99m}Tc are recorded in Table 2. The pertinent findings are: 1) A nonfunctioning mass occurred in 48.1% of the patients with neoplastic lesions (adenoma or carcinoma) in contrast to 6.5% of the patients with pathologically confirmed nodular goiter ($P < 0.005$). 2) A hypofunctioning mass was observed in 42% of the patients with pathologically confirmed nodular goiter and 37.0% of patients with neoplastic lesions (cancer or adenoma). 3) A hyperfunctioning mass was present in 13.5% of the 222 patients. Nine of these 30 patients were operated upon because of the size of the mass or because of asssociated hyperthyroidism.

Table 3 records information concerning the duration of the thyroid masses prior to diagnosis based upon history and/or physical examination. Twenty-five per cent of the patients with adenoma and 42.1% of the patients with cancer had a history of less than one month. The most significant finding is that patients with clinical and pathological diagnoses of nodular goiter had a relatively long history.

Table 4 records the results of the ^{75}Selenomethionine scans which were done in 94 patients. Of the patients with adenomas and cancer 47.6% had selective uptake of this radionuclide in the mass compared with 14.3% of patients with nodular goiter upon whom an operation

TABLE 3. *Duration of Solitary Nodule (Dominant Mass) in 222 Patients With Solitary Nodules (Dominant Masses) in the Thyroid Gland With a Clinical Diagnosis (No Operation) and a Pathological Diagnosis (Operation)*

		1 Month		2–3 Months		4–12 Months		1 Year	
	#	#	%	#	%	#	%	#	%
Clinical Diagnosis									
Cyst	8	4	50.0	2	25.0	1	12.5	1	12.5
Thyroiditis	8	4	50.0	2	25.0	1	12.5	1	12.5
Nodular Goiter	140	78	55.7	11	7.9	14	10.0	37	26.4
Total	156	86	55.1	15	9.6	16	10.3	39	25.0
Pathological Diagnosis									
Cyst	4	1	25.0	2	50.0	1	25.0	0	00.0
Thyroiditis	4	0	00.0	2	50.0	1	25.0	1	25.0
Nodular Goiter	31	9	29.0	1	3.2	4	12.9	17	54.8
Adenoma	8	6	75.0	0	00.0	0	00.0	2	25.0
Cancer	19	8	42.1	6	31.6	3	15.8	2	10.5
Total	66	24	36.4	11	16.7	9	13.6	22	33.3

TABLE 4. *^{75}Selenomethionine Scans in 94 Patients With Solitary Nodules (Dominant Masses) in the Thyroiud Gland With a Clinical Diagnosis (No Operation) and a Pathological Diagnosis (Operation)*

		Selective uptake		Diffuse uptake		No selective uptake	
	#	#	%	#	%	#	%
Clinical Diagnosis							
Cyst	2	0	00.0	0	00.0	2	100.0
Thyroiditis	1	1	100.0	0	00.0	0	00.0
Nodular Goiter	44	10	22.7	1	2.3	33	75.0
Total	47	11	23.4	1	2.1	35	74.5
Pathological Diagnosis							
Cyst	3	0	00.0	2	66.7	1	33.3
Thyroiditis	2	0	00.0	2	100.0	0	00.0
Nodular Goiter	21	3	14.3	0	00.0	18	85.7
Adenoma	4	2	50.0	0	00.0	2	50.0
Cancer	17	8	47.1	1	5.9	8	47.1
Total	47	13	27.7	5	10.6	29	61.7

was performed ($P < 0.05$). A localized uptake in 22.7% of the patients with clinically diagnosed nodular goiter suggested that other findings (history, physical, ^{125}I, ^{99m}Tc and ultrasonography) placed these patients in a low risk group.

Table 5 records the results of ultrasonography performed in 62 patients. Seven of the 8 patients with a diagnosis of a cyst had an echo-free mass. Findings consistent with a cyst were observed in one patient with an adenoma and in one patient with cancer. The latter patient had a cyst and a separate *occult* solid carcinoma. All 35 patients with a diagnosis of nodular goiter had a solid lesion as indicated by the ultrasonograms.

Table 6 compares the size of the dominant mass on physical examination with the findings on thyroid scan. In about one-third of the masses regarded as solitary on physical examination, the scans indicated a diffuse uptake of radionuclide. The physical findings indicated a larger lesion in adenomas whereas scan findings, a larger lesion in carcinomas.

Table 7 depicts the results of thyroid suppression in 65 patients (49 with a clinical and 16 with a pathologic diagnosis). This approach was most useful in identifying patients with nodular goiter and thyroiditis. Nine patients (presumed nodular goiter) had complete regression. This represents 20.9% of patients with a clinical diagnosis of nodular goiter and 17.6% of all patients with a diagnosis of nodular goiter. Three patients who did not respond to suppressive therapy proved to have adenoma and two patients had carcinoma. Neither of the latter patients had evidence of metastatic disease.

Discussion

Thirty years have passed since Cole's classic paper documenting the relatively high incidence of thyroid cancer in euthyroid patients with solitary or dominant masses in their thyroid gland. During this period there has been an increase in the clinical and autopsy incidence of this neoplasm.[5] When special techniques are used to evaluate the thyroid gland at necropsy an incidence of 5.7% has been reported.[24] Most of these cancers had little clinical significance and few were responsible for the death of the patient. The literature indicates an overall increasing incidence of thyroid cancer and an increasing incidence of cancer in patients operated upon for nodular goiter. This probably reflects better patient selection achieved by using a variety of criteria, both specified and unspecified.

Initially the solitary nodule constituted the primary indication for operation yielding an incidence of cancer in 4 to 25% of patients.[3,8,12,17] Currently the factors most commonly used to discriminate benign from malignant lesions include the age and sex of the patient, functional activity of the nodule, studies with B-mode ultrasonography and the results of suppressive therapy. These criteria have been used singly or in combination. With the ability to differentiate cysts, hyperfunctioning nodules, thyroiditis and TSH dependent nodular goiter, the number of operations for non-neoplastic lesions has declined with a higher yield of cancer.[3,17] Few authors, however, have improved on the results of Cole *et al.* who without the present methods of evaluation found an incidence of cancer in 11% of patients with multinodular goiter and 24% with solitary nodules.[8]

Radioiodide scanning for evaluation of patients with a nodular goiter was first reported by Dobyns in 1949.[14] He and Cope reported a higher incidence of cancer in patients with a low radioiodide content in a thyroid mass.[9] Others have reported similar findings.[20] The limitations of the scanning techniques in determining the intrinsic content of radioisotope in a nodule are well documented.[6] It is particularly difficult to appraise small nodules located deep in thyroid parenchyma. This is well illustrated in

TABLE 5. *Ultrasonograms of 62 Patients With Solitary Nodules (Dominant Masses) in the Thyroid Gland With a Clinical Diagnosis (No Operation) and a Pathological Diagnosis (Operation)*

		Cyst		Solid	
	#	#	%	#	%
Clinical Diagnosis					
Cyst	7	7	100.0	0	00.0
Thyroiditis	1	0	00.0	1	100.0
Nodular Goiter	24	0	00.0	24	100.0
Total	32	7	21.9	25	78.1
Pathological Diagnosis					
Cyst	1	0	00.0	1	100.0
Thyroiditis	1	0	00.0	1	100.0
Nodular Goiter	11	0	00.0	11	100.0
Adenoma	6	1	16.7	5	83.3
Cancer	11	1*	9.1	10	90.9
Total	30	2	6.7	28	93.3

TABLE 6. *Size of Solitary Nodule (Dominant Mass) as Determined by Physical Examination and ^{125}I or ^{99m}Tc Scans in Patients With Solitary Nodules (Dominant Masses) in the Thyroid Gland With a Clinical Diagnosis (No Operation) and a Pathological Diagnosis (Operation)*

	<2 Cm.				>2 Cm.			
	Exam		Scan		Exam		Scan	
	#	%	#	%	#	%	#	%
Clinical Diagnosis								
Cyst	4	57.1	4	80.0	3	42.9	1	20.0
Thyroiditis	2	66.7	1	100.0	1	33.3	0	00.0
Nodular Goiter	62	67.4	34	50.0	30	32.6	34	50.0
Total	68	66.7	39	52.7	34	33.3	35	47.3
Pathological Diagnosis								
Cyst	0	00.0	1	33.3	4	100.0	2	66.7
Thyroiditis	2	100.0	1	50.0	0	00.0	1	50.0
Nodular Goiter	9	39.1	17	68.0	14	60.9	8	32.0
Adenoma	3	37.5	4	50.0	5	62.5	4	50.0
Cancer	7	46.7	7	38.9	8	53.3	11	61.1
Total	21	40.4	30	52.6	31	59.6	27	47.4

the findings of Kendall and Condon who observed a 20.9% incidence of thyroid cancer in 91 patients.[19] The incidence of hypofunction was 80% in benign and 85% in malignant nodules. Scans were considered to be of no discriminating value. These investigators, however, did not differentiate between non and hypofunctioning masses or relate function to mass size. Nelson and Gorman indicate that radioisotope scanning is not helpful in evaluating cancer which is not palpable or masses less than 2 cm in diameter.[22] Oblique scanning techniques have recently been introduced to overcome the problem of the small nodule located within normal thyroid parenchyma.[2]

Our findings suggest that it is important to differentiate between nonfunctioning and hypofunctioning lesions. Dominant masses with no uptake of ^{125}I or ^{99m}Tc had about a 50% chance of being adenoma or carcinoma. When there was hypofunction the probability of adenoma or carcinoma was about the same as that of nodular goiter. In contrast, when the scan was interpreted as normal, hyperactive or other, the probability of either adenoma or carcinoma was greatly reduced.

In this study three historical factors were evaluated: duration of mass, sex and age of patient. Duration of the dominant mass and sex of the patient appeared to have some usefulness in discriminating between a benign and malignant lesion. Patients with adenoma and carcinoma had a shorter history of a mass than those with nodular goiter. The incidence of cancer in dominant masses in males (17.2%) was higher than comparable masses in females (7.2%). In view of the increasing incidence of nodular goiter with age the equal distribution of cancer and nodular goiter above and below 40 years of age was somewhat surprising. This may be a reflection of the average age at diagnosis of well differentiated thyroid cancer (45.7 years)[4] and the unconscious exclusion of older patients with nodular goiter from this type of evaluation. The higher incidence of nodular goiter in older people suggests that after 40 years of age there should be additional findings before such patients are considered at risk from thyroid cancer.[3]

Ultrasonography has been a reliable method to detect cysts in the thyroid gland. Aspiration, combined with

TABLE 7. *Response to Suppressive Therapy in 65 Patients With Solitary Nodules (Dominant Masses) in the Thyroid Gland with a Clinical Diagnosis (No Operation) and a Pathological Diagnosis (Operation)*

		None		Partial		Complete		Progression	
	#	#	%	#	%	#	%	#	%
Clinical Diagnosis									
Cyst	0	0	00.0	0	00.0	0	00.0	0	00.0
Thyroiditis	6	4	66.7	2	33.3	0	00.0	0	00.0
Nodular Goiter	43	23	53.5	9	20.9	9	20.9	2	4.7
Total	49	27	55.1	11	22.5	9	18.4	2	4.1
Pathological Diagnosis									
Cyst	1	1	100.0	0	00.0	0	00.0	0	00.0
Thyroiditis	2	2	100.0	0	00.0	0	00.0	0	00.0
Nodular Goiter	8	6	75.0	0	00.0	0	00.0	2	25.0
Adenoma	3	3	100.0	0	00.0	0	00.0	0	00.0
Cancer	2	2	100.0	0	00.0	0	00.0	0	00.0
Total	16	14	87.5	0	00.0	0	00.0	2	12.5

histologic study of the fluid content, eliminates the need for an operation in most of these patients. In the development of refinements in the method of B-mode ultrasonography cystic areas as small as 1–2 mm may be detected. The accuracy of this approach is estimated to be greater than 90%.[23] The incidence of cysts in patients with a "solitary thyroid nodule" has been reported to be from 7 to 25%.[1,2,23] Data are still being accumulated with this new noninvasive technique. It is too early to give precise figures as to the incidence of cancer in cystic lesions. In view of the observation that most cysts represent degenerative changes in nodular goiters the incidence of cancer is probably quite low. However, some well differentiated carcinomas may have a cystic component and may present as a "mixed" cyst.[1]

Our findings indicate that when there is an increased uptake of ^{75}Selenomethionine in a dominant nodule there is about a 50% incidence of either adenoma or carcinoma. The increased uptake noted with chronic thyroiditis is usually diffuse in contrast to the localized uptake in neoplasms. Our overall experience indicates approximately ⅓ of patients with neoplasms will have a false negative scan.

Hill called attention to the value of suppressive therapy as a discriminating factor in differentiating benign from malignant thyroid lesions.[17] He observed a 4% incidence of thyroid cancer (683 patients; 1950–1960) when most patients with thyroid nodules were operated upon. During 1960–63 suppressive therapy was used to help select patients for operation. During this time the incidence of thyroid cancer in 159 patients was 12.6%. Since 1964 suppressive therapy has been used as a routine except in patients under 16, over 65 with a new nodule, who were symptomatic, had prior irradiation or obvious metastases. In 167 patients using these criteria the incidence of cancer was 36.5%. Unfortunately, Hill did not specify the number of patients on suppressive therapy who had regression of their thyroid masses or the incidence of regression in cold or hypofunctioning masses. In our studies some degree of regression occurred in approximately ⅓ of patients with nodular goiter on suppressive therapy. No regression occurred in patients with an operative finding of adenoma or carcinoma.

Brooks used a number of criteria to improve the selectivity of patients undergoing operation for thyroid cancer.[3] He reported a cancer incidence of 9% in 502 patients operated upon between 1940 and 1962. Of patients without cancer, 60% had nodular goiter, 26% adenoma and 5% thyroiditis. He restricted operations to: A) males of all ages not responding to suppressive therapy; B) females below the age of 40 with cold nodules not responding to suppressive therapy; and C) females over 40 if there was an increase in nodule size on suppressive therapy, or in whom a needle biopsy was positive in a large or clinically suspicious nodule. Using such criteria, there was an increase in the overall yield of thyroid cancer to 19% in 202 patients so managed. The remaining patients had a 42% incidence of nodular goiter, 38% incidence of adenoma and 1% incidence of thyroiditis. Brooks points out that less than 1% of patients had regression of their nodules on suppressive therapy. Thus, other criteria for selection of patients for operation must have been used.

The variability in the recorded incidence of cancer in solitary or dominant thyroid masses and in nontoxic nodular goiters continues to be substantial. It is evident that in absence of histologic proof there is no one criterion, that is of unequivocal predictive value in establishing the diagnosis. There is evidence that the application of the methods described in this report can produce a more accurate clinical diagnosis and thus eliminate a certain number of unnecessary operations in patients with benign thyroid disorders. Thyroiditis, cysts and hyperfunctioning nodules can usually be excluded by clinical findings supplemented by laboratory studies. Clinically adenoma has the same characteristics as well differentiated cancer. Differentiation between these two entities can only be made by histologic study. Basically the problem is to distinguish between nodular goiter and benign and malignant thyroid tumors. Thirty per cent of the 222 patients with dominant masses included in this study ultimately were operated upon. This is a relatively low operation rate in patients with dominant thyroid masses. Of the patients operated upon, 40% had either a benign or malignant neoplasm with well differentiated cancer being present in 29%. In over two-thirds of these patients the diagnosis was made on clinical data and was not substantiated by histologic findings. Were pathological findings available, some of these patients might fall into other categories.

Conclusions

The most discriminating criteria for the differentiation of thyroid cancer from benign lesions were: 1) *Sex*: 17.2% of all males in the study and 50% of those operated upon proved to have thyroid cancer. This was true of only 7.3% of all females and 25% of those operated upon. 2) *Functional status via* ^{125}*I or* ^{99m}*Tc scan*: Nonfunction was present in 47.4% of patient with cancer compared with 7.6% of patients with adenomatous goiter. Hypofunction was not helpful in discriminating between cancer and adenomatous goiter; however, the incidence of cancer with hypofunction was about 10 fold that in patients with scans interpreted as showing normal, other or hyperfunction. 3) ^{75}*Selenomethionine scan*: 47.0% of patients with cancer proved to have a selective concentration of this radionuclide compared with 20.0% of patients with adenomatous goiter. 4) *Ultrasonography* was useful in differentiating solid from cystic lesions. 5) *Regression on suppressive therapy* was useful in identifying TSH dependent nodular goiter.

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DISCUSSION

DR. ERNEST A. GOULD (Washington, D.C.): Our interest in the problem has worked out much the same way, except that we are not as rigid in our criteria. We get somewhat edgy about our internists and endocrinologists procrastinating with these people with unilateral masses.

All too often, we feel that even though the mass is unilateral, the internist waits a little too long on the patient who has the solid tumor. If the surgeon had seen the patient earlier, he probably would have made a quicker decision to bring the patient to the operating room. We find that even where there is complete regression of the dominant unilateral lobe, with a remaining solitary nodule, 30% of them will turn out to be multinodular goiter. On the other hand, there is a 5% incidence of malignant tumors in this group.

With all of our sophisticated methods today, the solitary unilateral nodule deserves surgical attention; and although we may reduce some of the incidence of surgery in this unique group, surgical therapy is the treatment of choice.

DR. JOSEPH A. BUCKWALTER: (Closing discussion) Because of the limited time for his presentation, Dr. Thomas was unable to discuss in depth our method of disposition of patients with thyroid nodules. He presented the guidelines which we use which are modified as indicated by the findings unique to each patient.

We have seen no patients with regression on suppressive therapy who ultimately were found to have cancer.

In support of the use of suppressive therapy, it should be noted that all patients with cancer in our study had the well differentiated variety. Almost always the clinical characteristics of poorly differentiated carcinoma are sufficiently typical to permit a correct diagnosis prior to biopsy or operation. Because of the indolent, long course of patients with well differentiated carcinoma, a more conservative approach is justified.

(Slide) Another clinical feature studied was the time that the mass had been present prior to examination. Patients with adenoma and carcinoma had a known mass or nodule in their thyroid for a shorter period of time than those with nodular goiter.

During the four years, three months of the study, we saw a total of 60 patients with carcinoma of the thyroid. Thus, the study included one-third of the patients seen with well differentiated thyroid.

Myxoma of the Heart:

Clinical and Experimental Observations

PANAGIOTIS N. SYMBAS, M.D., CHARLES R. HATCHER, JR., M.D., MICHAEL B. GRAVANIS, M.D.

From the Joseph B. Whitehead Department of Surgery,
Thoracic and Cardiovascular Surgery Division,
and the Department of Pathology,
Emory University School of Medicine
and Grady Memorial Hospital, Atlanta, Georgia

During the past 12 years, 13 patients with atrial (10 left and 3 right) myxoma have been treated. The tumors of the left atrium produced signs and symptoms of mitral valve obstruction and/or subacute bacterial endocarditis and those of the right atrium manifestations of tricuspid valve disease or of pulmonary embolus or hypertension. The diagnosis was established by angiocardiography in 8 patients, at surgery performed for suspected mitral stenosis in 3 patients, and at autopsy in 2 patients. Resection of the atrial myxoma alone in 5 patients or with atrial septum where the atrial myxoma was attached in 4 or with the whole right atrial wall where the atrial myxoma was attached in one patient was performed and all are doing well without evidence of recurrence. Studies of experimentally produced 1.5–3 cm in diameter left atrial thrombus in 30 dogs divided into 5 groups and followed cineangiocardiographically and sacrificed from 14 days to 6 months indicated that the implanted thrombus is absorbed over a 3 to 6 month period. These experimental and human left atrial thrombi were found to be histologically and histochemically different from human atrial myxomas. The electron microscopic studies performed on some of the resected atrial myxomas suggested that the atrial myxoma cells are active cells of endothelial origin. These observations suggest that atrial myxoma is a primary tumor of the heart which can mimic other clinical entities, and the results of its surgical treatment are gratifying and long lasting.

MYXOMA OF THE HEART is the commonest intracavitary tumor accounting for more than half of all primary cardiac tumors.[1,11] The clinical manifestations of these tumors are variable and despite the increase of clinical awareness and improved diagnostic techniques, still their diagnosis occasionally appears as a surprise at surgery or autopsy.[2,3,19] Also, despite several histochemical[5,6,17] and structural studies[10,14,18,20] of cardiac myxomas, the cell of origin, and certain of the structural features of these tumors remain subject of controversy.

This communication is a review of our clinical experience and of the possible histogenesis of atrial myxoma.

Material and Methods

Clinical Studies

During a 12-year period, 1962 to 1974, 13 patients (5 men and 8 women) with atrial myxoma were treated at Emory University and Grady Memorial Hospitals. Aspects of several of these patients have been reviewed previously.[16] Ten of the tumors arose from the left atrium and 3 from the right atrium, one of which protruded into the left atrium through an atrial septal defect. In 9 patients the presenting clinical picture was suggestive of mitral valve disease, in most of them of mitral stenosis, and two of them had, in addition, constitutional symptoms (malaise, fever, anemia, etc.) suggestive of subacute bacterial endocarditis. Left atrial myxoma was suspected in 3 of these patients initially and in 2 after unsuccessful treatment for bacterial endocarditis and was proved by angiocardiography. In the remaining 4 patients, an unexpected atrial myxoma was found in 3 at the time of thoracotomy for mitral commissurotomy and in one at autopsy while awaiting

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"closed commissurotomy." One patient complained of dyspnea and his chest roentgenogram and angiocardiogram showed a calcified myxoma in the right atrium and one had chest pain and hemoptysis which were initially thought to be due to pulmonary embolus alone but later a right atrial myxoma was diagnosed angiocardiographically.

Another patient was seen with dyspnea, severe cyanosis and grade 2/6 systolic murmur. This clinical picture was initially thought to be the result of pulmonary hypertension, but angiocardiography revealed the cause to be a right atrial myxoma protruding into the left atrium through an atrial septal defect (Fig. 1).

One patient was admitted with clinical and electrocardiographic findings indicative of acute myocardial infarction and died shortly after admission. At autopsy, an unexpected left atrial myxoma was found in addition to the acute myocardial infarction.

Eleven of the atrial myxomas were globular or ovoid, pediculated, arising from the atrial septum in the vicinity of the fossa ovalis and two were botryoid with broad attachment site, one of which was attached to the whole right atrial wall.

Five of the operated upon patients had resection of their tumor only with its pedicle, four had resection of the tumor and of the atrial septum where the myxoma was attached and one had resection of the tumor, the intra-atrial septum and the right atrial wall because the tumor was attached to all these structures. (Fig. 2). There was no operative mortality in the 10 patients who had resection of their atrial myxoma and all are doing well, without evidence of recurrence of the tumor, one to 12 years after surgery. One patient died while awaiting reoperation for resection of the left atrial myxoma diagnosed at the time of thoracotomy for suspected mitral stenosis. One patient died from myocardial infarction and another while awaiting "closed commissurotomy," and at autopsy an unexpected left atrial myxoma was found in both.

The light microscopic study of all resected tumors revealed abundant mucoid stroma, varied cellularity, from area to area along with areas of fibrosis and hemorrhage. The myxoma cells, singly or in clumps, lay in pools of mucoid stroma and they varied in shape from round to spindle to stellate.

Electron microscopic studies were performed in three of the resected myxomas, all of which showed the myxoma cells with fairly distinct nucleolus, often dilated endoplasmic reticulum, intercytoplasmic filaments, fat droplets with glucogen and plentiful collagen around the cells. In numerous cells, multiple Golgi apparatuses and prominent mitochondria were present.

The histochemical studies of 4 of the examined myxomas showed that the tumors ground substance was composed of only hyaluronic acid and chondroitin-4 or chondroitin-6 sulfate.

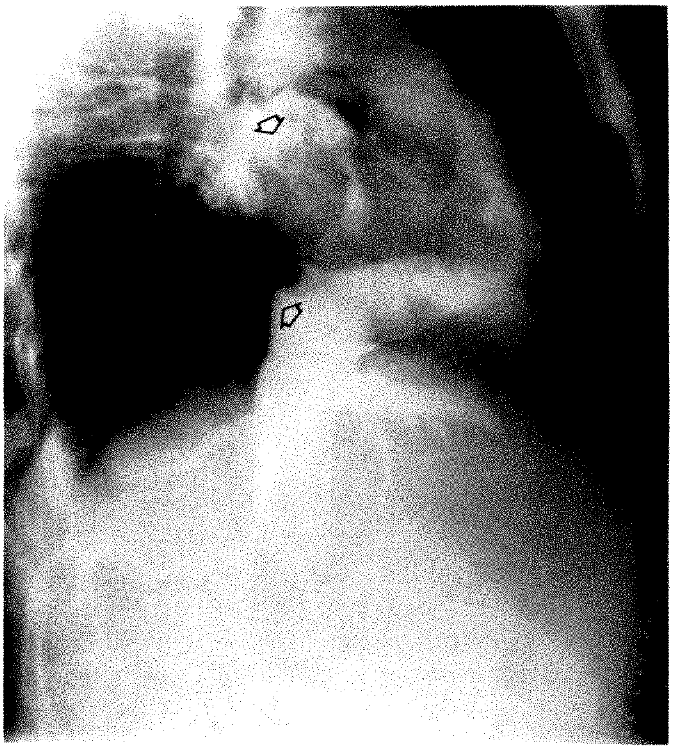

FIG. 1. Posteroanterior and right lateral biplane angiocardiograms showing a large filling defect in the right atrium and an early opacification of the left atrium by contrast material traversing the atrial septal defect.

Animal Studies

In 30, healthy, adult mongrel dogs, under inflow cavae occlusion, right atriotomy and atrial septotomy a 1.5–3 cm in diameter Surgicel* ball appropriately constructed was sutured in the left atrium at the superior margin of the fossa ovalis.

At ten days after operation and at monthly intervals thereafter, serial cineangiocardiograms were obtained injecting into the main pulmonary artery 20 ml of Renovist† at 200 p.s.i.

The dogs were sacrificed and autopsied: group I, 10 dogs, 2 to 14 days after operation; group II, 5 dogs, one month; group III, 5 dogs, 2 months; group IV, 6 dogs, 3 months and group V, 4 dogs, 4 to 6 months after operation. The Surgicel thrombus with the adjacent septum was removed at the time of autopsy and histological and histochemical studies were performed.[4]

The cineangiocardiograms showed, with the passage

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* Oxidized regenerated cellulose, Johnson & Johnson, New Brunswick, New Jersey 08903.

† Renovist, E. R. Squibb & Sons, 909 Third Avenue, New York, New York.

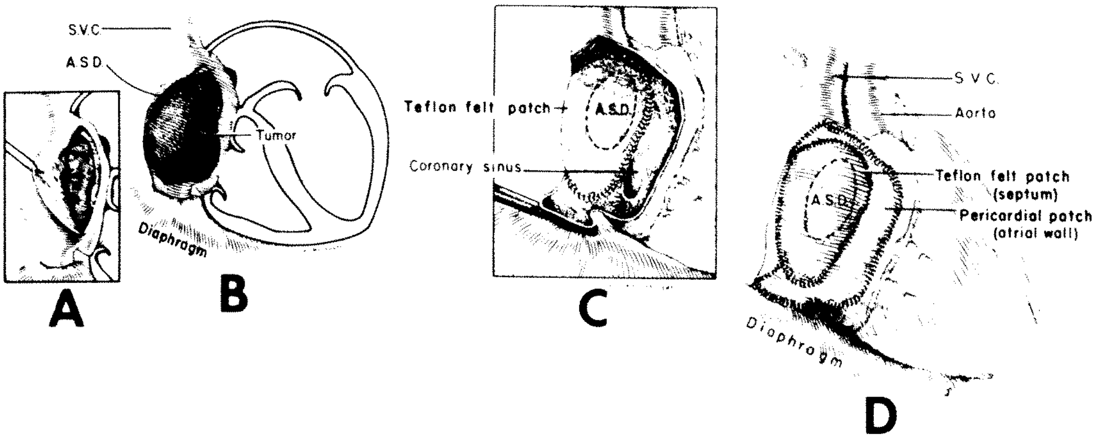


FIG. 2. Drawings, a) and b) of the right atrial tumor and c) and d) of the technique employed to reconstruct the new right atrium.

of time, progressive diminution of the filling defect in the left atrium (Fig. 3).

The implanted Surgicel ball was examined grossly and histologically: in group I dogs there was a large ball of thrombus; in group II dogs a somewhat smaller thrombus with smooth endothelial-like surface, which on histological examination, was a well-organized thrombus (Fig. 4a); in groups III and IV the thrombus was progressively smaller and an increasing prominent connective tissue developed around the thrombus and invaded it (Figs. 4b and 4c). In group V dogs fibrous tissue had replaced the thrombus (Fig. 4d).

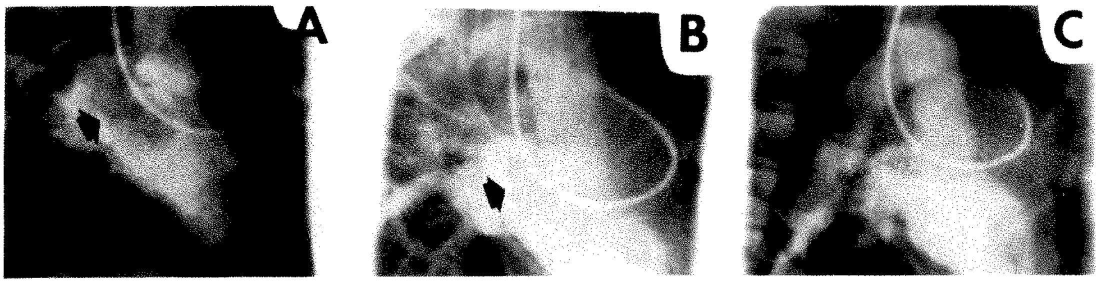
The histochemical studies of the implanted aging thrombus suggest the presence in the ground substance, in addition to hyaluronic acid, chondroitin-4 and chondroitin-6 sulfates, other glycosaminoglycans, such as dermatan sulfate, keratan sulfate, or heparan sulfate.

Discussion

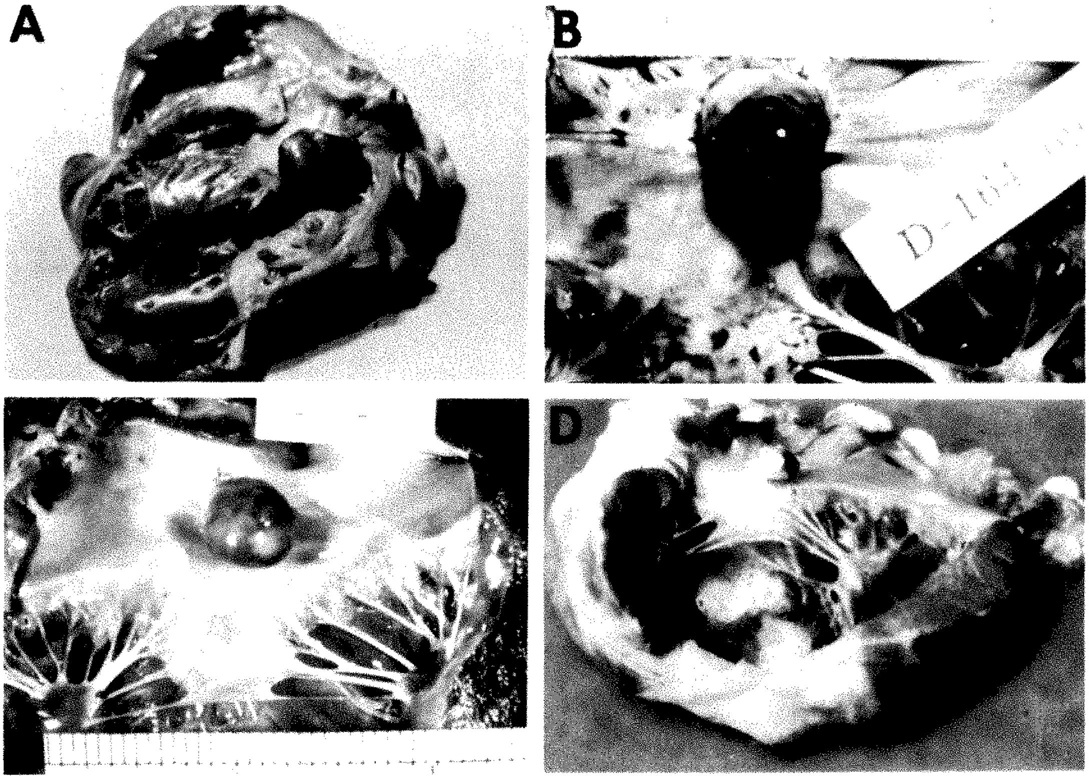
Myxoma of the heart can now be successfully treated but the success is obviously dependent upon the correct diagnosis and treatment prior to development of catastrophic complications such as sudden death, embolism or cardiac failure. Awareness, therefore, of this cardiac tumor, familiarity with its various clinical manifestations, and prompt and proper treatment are essential for the successful treatment.

Myxoma of the heart is the commonest primary cardiac tumor most frequently occurring in the left atrium at the fossa ovalis. The right atrium or both the right and left atrium and the left or right ventricle are other sites of origin of this tumor. Myxoma of the heart occurs in all ages from newborns to 80 years old; but most commonly it is found between 30 and 60 years of age, and it is more frequent in women. The presenting clinical picture of the cardiac myxoma is most variable and is dependent to a certain extent on the location of the tumor.[9] Symptoms and signs of mitral valve lesion, usually mitral stenosis with or without symptoms of subacute bacterial endocarditis are the most common manifestations of left atrial myxoma, resulting not infrequently in the erroneous diagnosis of mitral stenosis or subacute bacterial endocarditis. Symptoms of tricuspid stenosis and pulmonary hypertension are the frequently seen clinical manifestations, of right sided, usually right atrial myxoma. Systemic embolization from left atrial myxoma and rarely pulmonary embolization from a right one may also be part of the clinical picture emphasizing the need for consideration of this clinical entity when there is no apparent explanation of these embolizations and for the histological examination of the extracted emboli.

In many patients cardiac myxoma provokes constitutional manifestations characterized by weight loss, fatigue, fever, anemia, high sedimentation rate and elevated serum immunoglobulin concentration, leukocytosis, thrombocytopenia, clubbing, Raynaud's phenom-



FIGS. 3a to c. Cineangiocardiograms, a) shortly after implantation of the left atrial thrombus; b) 40 days later, and c) 70 days later.



FIGS. 4a to d. Experimental left atrial thrombus, a) one month old, b) two months old, c) three months old, and d) six months old.

enon, and breast fibroadenomata. In addition, right atrial myxoma has been the cause of polycythemia and cyanosis.

The diagnosis, therefore, of atrial myxoma should be suspected in a patient who has various features of classic triad of atrioventricular valvular obstructive disease, of embolism and of constitutional manifestations. This is especially true in patients with clinical findings of heart disease and history of syncope or dizziness and a marked postural effect on the severity of symptoms and especially if recumbency relieves dyspnea or with variable auscultory findings with position changes or change from one examination to the next or with early diastolic sound termed as "tumor plop".[8] The diagnosis, however, can be only established with echocardiography[13] and especially with angiocardiography, although these tests will not differentiate atrial myxoma from thrombus.

Angiocardiography should be done in all patients suspected of having myxoma of the heart. In order to avoid provocation of tumor embolization, the radiopaque material should be injected into the cavae for visualization of right atrial myxoma and into the pulmonary artery for the diagnosis of myxoma of the left atrium.[15]

Once the diagnosis of left atrial myxoma has been made, the patient should be operated upon as soon as possible before undesirable complications, embolization or sudden death occur. An 8% mortality has been reported in patients awaiting operation following definitive diagnosis.

The cardiac tumor should be removed under direct vision and total cardiopulmonary bypass. Both left or right atrial myxomas are approached through right anterolateral or midsternotomy incision and moderate hypothermia. In order to prevent undue handling of a right atrial myxoma in some patients, the inferior vena cava might need to be drained through femoral vein cannulation and the superior vena cava through the axygos vein or through a high incision of the right atrial wall. Gentle handling of the heart during cannulation, constant decompression of the left ventricle through apical vent, electrical fibrillation after initiation of cardiopulmonary bypass and before any manipulation of the tumor, en bloc removal of the myxoma without fragmentation, and irrigation and aspiration of the atrium and ventricle with saline to wash out any tumor fragments are of paramount importance to prevent catastrophic embolization of tumor debris.

After excision of the tumor, the adjacent to it mitral and tricuspid valve should be evaluated for any abnormality and both atria examined for multicentric myxoma. Although the excision of the area of the septum where the myxoma is attached has been a controversial point, many authors now feel it is preferable and provides protection against the rare incidence of recurrence of the myxoma.[7] Read et al.[12] found 8 reports and described 3 of their own cases with recurrence of this cardiac tumor.

Since cardiac myxoma was first recognized, a controversy has existed regarding its histogenesis, thrombotic[4] or neoplastic in origin. The histochemical, light and electron microscopic findings of the present study show no evidence to support the contention that myxoma of the heart evolves from cardiac thrombus nor that its cells are modified muscle cells. Although there is electron microscopic evidence that precollagent may be synthesized by the myxoma cells, the production of mucoprotein rich matrix does not help in identifying the cell or origin, since many cells are capable of synthesizing these substances. The presence, however, of numerous intracytoplasmic fibrils favors an endothelial or basoformative cell origin. This cell origin is strengthened even more by the existence of lipid droplets within the cytoplasm of the cells concerned.

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DISCUSSION

DR. HARRIS B. SHUMACKER, JR. (Indianapolis): Dr. Symbas and his colleagues have made a significant contribution by relating their clinical experiences with this interesting, life-threatening, and operatively curable intracardiac tumor, and by describing their pertinent experimental observations.

All of our treated cases have been recognized preoperatively, and have done well, and have exhibited no evidence of recurrence.

As Dr. Symbas has mentioned, patients harboring these lesions ordinarily obtain professional aid because of cardiac dysfunction. In rare instances, however, they seek medical, and soon surgical help, because of other manifestations, as was the case with one of our patients, who suddenly developed frightening visual disturbances consequent to a retinal arterial embolus from a partially calcified myxoma.

Sometimes, too, the lesion can be identified by old and simple methods. If the tumor is pedunculated and contains calcium, one can, on the ordinary fluoroscopic screen, see it flip from atrium to ventricle and back again with each heart beat.

In my judgment, the greatest advance in the management of myxomas has perhaps been medical, rather than surgical. I refer to their precise, almost instant recognition by the simple bedside technique of echocardiography.

My institution was among the first to explore the use of ultrasound as a cardiac diagnostic tool, and I feel confident in saying that since the first myxoma was so studied, each one has been identified positively by this technique. So certain am I of its accuracy that I would operate with confidence on any lesion so diagnosed, without any other studies such as cardiac catheterization if operative intervention were fairly urgent. This has proven a life-saving measure. I recall well one patient, practically moribund when first seen, in whom immediate operation could be carried out after promptly establishing the diagnosis in this way. It is almost certain that she would not have survived long enough for other studies to have been done, such as cardiac catheterization.

DR. GILBERT S. CAMPBELL (Little Rock, Arkansas): Dr. Symbas and his associates are to be commended for their elegant experimentation and careful clinical studies, which clearly demonstrate the neoplastic nature of cardiac myxomata. Even though in half of their cases the tumor was just plucked, they report that all obtained a "gratifying and long-lasting" result. Others have not had such a happy experience.

Thus, as my colleague, Dr. Raymond Read reported last year, 16 patients are now known to have suffered 19 recurrences, after what was thought to be "successful" removal of the left atrial myxomata.

(Slide) This shows the resected tumor in one of our patients. You can see from the photograph that quite a bit of the atrial septal wall was removed with the tumor. He returned nine years later with obvious metastases in the chest wall. The following year he had parascapular metastases, and one year later he died. Autopsy revealed metastasis to the tongue, lungs, more tumor in the heart, and in the thoracic wall.

Another of Dr. Read's patients has had two local recurrences in the left atrium, and is now doing well nearly two years after his last operation, which was followed by a course of Adriamycin. We recommend radical excision of the atrial septum to reduce recurrence from multicentric foci. Extraseptal myxomata are more likely to recur, and on histological study these recurrences have what appears to be a progressively more malignant nature.

Strong efforts should be made to prevent myxomatous emboli, since they can invade locally. These tumors may be multiple and can spread to other heart chambers. Therefore, other chambers of the heart should be inspected at the first operative procedure. Since the malignant potential of these neoplasms has been established, postoperative study with echo cardiography is an excellent noninvasive technique for following these patients (as suggested by Dr. Schumacker). This followup with echo cardiography needs to be very rigorous.

Dr. Allen S. Hudspeth (Winston-Salem): I think that this tumor probably is more common than we have thought in the past. I know the more echo cardiographic studies that are done of the cardiovascular system, I believe, the more you are going to see this tumor. All our patients are screened now with echo cardiography, particularly patients whose cardiologists are following with "mild mitral stenosis." I have removed two of these tumors in the past month, picked up like this, with mild symptoms.

I think the concept that's been mentioned also about the removal of the entire tumor along with part of the septum is important.

I want to show a couple of slides about the surgical aspects of removing these tumors. Removing the left atrial myxoma is a relatively simple operation. However, there are definite hazards associated with it. I think the main risk is air embolism. There is some risk of tumor embolism. The tumor may be fragmented, or incompletely removed.

I have tried various ways of removing these tumors, and I would like to show you the technique I have settled on as what I think is the easiest and safest way to do it.

(Slide) If you clamp the aorta, and use topical hypothermia, completely arrest the heart, then you can operate with leisure, in a bloodless, quiet field. If you don't do this, you may make some mistakes in removing this tumor. Most of these patients have a normal size heart. The right atrium is small, the left atrium is small, and the atrial septum is small: and if you go the various ways that we classically do to approach the septum, and so on, you may get disoriented. You can cut into this tumor, and so on, which might cause some difficulty.

What I think is the best way to approach this structure here (indicating) is the right superior pulmonary vein. If you make a linear incision on the right superior pulmonary vein for about 1–1½ cm, you will look directly into the left atrium. And if the heart is empty, you can very readily see the edge of this tumor. Then I cut on to the right atrial free wall, and then cut directly into the septum; and this gives excellent exposure, even when the heart is small.

(Slide) You can then, very readily, by being partly in the right atrium, partly in the left atrium, cutting down the septum toward the fossa ovale—you can see and control the removal of this tumor very readily.

(Slide) As you see, you can with ease see exactly where you are. You can make this septal defect into a pretty linear defect, rather than a ragged hole. Then, once, this tumor is removed, the fossa ovale is here—they are virtually always attached to the fossa ovale—and then you can lift this out, and then, by the suture technique of your choice, start at this end of the atrial septal defect, come down onto the pulmonary vein, completely closing the septum, obviously using the normal precautions for removing air, and so on, from the left side of the heart, and then continue this suture closure of the right atrium.

(Slide) This shows this particular tumor removed. There is a good margin of normal atrial septum with this.

Dr. John L. Ochsner (New Orleans): I'd like to share with you the blood supply of this tumor, which, as far as I know heretofore has not been described.

(Slide) As you know, there has been some question in the past as to whether this is a true neoplasm. This is an angiocardiogram just showing the typical tumor.

(Slide) The coronaries were injected, and you can see, at the beginning of the right coronary artery is a very large septal branch, going this way.

(Slide) Here you can see it then filling the tumor. This entire area (indicating) is the tumor.

(Slide) Here is the blush of the entire tumor at a later phase.

This, to us, proves without any doubt that this is a true neoplasm, and that it has a very large compensatory blood supply from a large septal branch off the right coronary artery.

Dr. Watts R. Webb (Syracuse, New York): I think we have had a very excellent presentation and discussion of this entity, which has so many protean manifestations. I certainly agree with the previous speakers that we have gone to routine echo cardiography in any of the patients that have any abnormal presentation of mitral stenosis.

The other thing that we would like to add, and emphasize, as Dr. Ochsner has, is that the coronary arteriography is of great value to you in showing the tumor blush, and often seeing the multiplicity of vessels that may give you some hint ahead of time of the rare one of these that may be malignant. I can assure you, this is no place to try to do a radical resection of a malignant tumor, because you end up with more than you can possibly reconstruct, if you try to take it out. Fortunately, they are very radiosensitive.

The two tumors you have seen presented on slides are a little bit different from many. Many of them are very villiform, filamentous, and you can see when you look at them how easily and readily they would produce emboli.

One of the more unusual presentations that we've had was in a beautiful young girl who was having a peculiar syndrome of multiple, recurrent cerebral arteritis. We didn't know whether it was lupus or periarteritis nodosa, or what was going on, until finally one of the little episodes of arteritis apparently involved the dorsalis pedis. We got a biopsy of this,and the pathologist was able to say: This looks like myxoma of the heart.

Sure enough, we were then eable to demonstrate it by echo cardiography, and remove it, leading to a complete recovery.

Dr. P. N. Symbas (Closing discussion): Dr. Shumacker, our cardiologists, too, are using the echocardiography for the diagnosis of this cardiac tumor as well as for the diagnosis of thrombus of the left atrium, particularly in patients with mitral stenosis but they also like to have angiocardiographic confirmation. Perhaps, echocardiographic demonstration of the tumor is sufficient for its diagnosis but in our institution is not used exclusively.

As far as the systemic embolization from this tumor which was mentioned by Dr. Webb, indeed, it is one of its manifestations but it was not seen in our group of patients.

Dr. Read's excellent report of malignant cardiac myxomas mentioned by Dr. Campbell enforces the hypothesis that myxoma of the heart are primary tumors.

Dr. Oschner's angiographic demonstration of large vessel feeding the myxoma is very interesting but I do not know whether we can use it as evidence to support the thesis that this cardiac tumor is a primary one. This is because Dr. Salyer in his recent report in the January issue of the *American Heart Journal* theorizes that cardiac myxoma originate from a thrombus in a low pressure cardiac chamber which is invaded by granulation tissue and its growth continuous due to influx of fluid into the lesion because of the differential pressure created between the new vessels of the thrombus and the cardiac cavity. So, he might use the observed by Oschner large vessel in favor of his hypothesis but I think our experimental work with our histochemical and electronmicroscopic findings strongly suggest that the myxoma of the heart is a primary tumor.

I appreciate Dr. Hudspeth's comments that we have to be very careful during the introduction of cardiopulmonary bypass because the greatest catastrophe that can occur during surgery of this curable lesion is a dislodgement of thrombus or tumor fragment and embolization into the brain. Time did not permit to go into operative details but we use some of his intraoperative maneuvers and sometimes in right atrial myxoma it is advisable to cannulate the inferior vena cava through the femoral vein and the superior through the axygos vein rather than through the right atrium so that with the introduction of the cannulus the tumor would not be fragmented and embolized.

Sphincteroplasty and Choledochoduodenostomy for Benign Biliary Obstructions

ROBB H. RUTLEDGE, M.D.*

Both sphincteroplasty and choledochoduodenostomy are valuable for choledocholithiasis, stenosis of the terminal bile duct, and occasional cases of pancreatitis. Selection of patients, technical details, and advantages and limitations of both operative procedures are presented. In a personal series of 600 benign biliary operations 73 patients had a sphincteroplasty or choledochoduodenostomy. Sixty of these had a sphincteroplasty without operative mortality, serious complication, or recurrence of biliary problems although 5 still have pain. A positive morphine-prostigmine test was a prime indication for surgery in these 5 patients. The evocative tests are now negative. Thirteen patients had a choledochoduodenostomy without mortality or significant complication. Twelve are symptom free but one has a "sump syndrome." Sphincteroplasty has been preferred because it gives dependent drainage, direct inspection of the ampullary area, and facilitates removal of impacted stones and debris. It is not always applicable and choledochoduodenostomy has been chosen in elderly poor risk patients or in those with pancreatic inflammation or periampullary duodenal diverticula. Both operations have specific advantages and limitations such that the surgeon should not use one to the exclusion of the other.

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BOTH TRANSDUODENAL SPHINCTEROPLASTY and choledochoduodenostomy are valuable in the treatment of benign biliary obstructions. The procedures are not necessarily competitive, although in many cases they probably could be used interchangeably.[43,44,48] Each has specific advantages and limitations. Each requires meticulous technique to achieve good results with minimal mortality. The purpose of this article is to report my experiences with these operations.

Benign Biliary Obstructions

For this presentation benign biliary obstructions include only those of the distal bile duct due to stones, stenosis of the papilla of Vater, or recurrent pancreatitis. Malignant obstructions, bile duct injuries, and other strictures are not included.

Most common duct stones come from the gallbladder but some are formed primarily in the duct because of stasis. Partial obstruction of the bile duct causes dilatation, biliary stasis, bactibilia, an increase of insoluble bilirubin, and the formation of sodium bilirubinate stones.[36,44] Adequate treatment of bile duct stones requires the correction of any biliary stasis as well as removal of the stones.

Stenosis at the ampulla of Vater is usually secondary to inflammation in the biliary area causing fibrosis and stricture of the papilla and sphincter of Oddi. Occasional primary cases of papillary stenosis occur without disease in the rest of the biliary tree. Microscopic diagnosis of papillary stenosis is difficult and confusing. Polarized light examinations to confirm the presence of collagen have helped clarify the findings.[1] Frequently stenosis of the papilla is a clinical diagnosis and is not confirmed by microscopic studies.[32]

A few cases of recurrent pancreatitis are caused by papillitis with fibrosis and stricture of the papilla.[31] Pancreatograms in these show an open dilated pancreatic duct without other obstructions. Originally sphincteroplasty was used to treat many cases of pancreatitis, but only these few will benefit.[2] The greatest use of sphincteroplasty is to prevent recurrent common duct stones and correct ampullary stenosis.[17]

Clinical Material

From 1960 through 1974 the author has performed 600 benign cholecystectomies or bile duct explorations.

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Four hundred and twenty-five had only a cholecystectomy, nearly always with an operative cystic duct cholangiogram. One hundred seventy-five patients had a common duct exploration. Of these 175 patients, 73 had either a sphincteroplasty or a choledochoduodenostomy and 102 had a common duct exploration without ablation or bypass of the sphincter. Thus 29% of the entire series has had some procedure on the common duct. Forty-two per cent of those whose ducts were explored had either a sphincteroplasty or a choledochoduodenostomy. One of these two operations was done on 12% of the entire series.

The subject of this report is the 73 patients having more than a common duct exploration. Sixty had a transduodenal sphincteroplasty and 13 had a choledochoduodenostomy. They are all private patients and none has been lost to followup. Nearly all of the patients have had a recent office visit and examination. Only rarely has the checkup been by a personal telephone call. Laboratory studies have been done on all symptomatic patients and include intravenous cholangiograms, upper gastrointestinal series, morphine-prostigmine tests and bilirubin, alkaline phosphatase and amylase levels.

The vast majority of these patients were having their first biliary operation. The usual surgical indication was stones or papillary stenosis rather than pancreatitis. This is quite different from a large referral center where more of the patients have pancreatitis and are having their second or third bile duct exploration. Consequently the impressions and results may not be the same.

Selection of Patients

Selection of patients that will benefit from either a sphincteroplasty or choledochoduodenostomy as either a primary or secondary procedure is difficult and inexact. Drouin[8] has pointed out that the gallbladder and sphincter of Oddi are paired structures. Animals like the horse, deer, rat and pocket gopher that have no gallbladder have no sphincter.[33] If the gallbladder is removed there is no physiological need for the sphincter, so he recommends a routine sphincteroplasty with each cholecystectomy. Unfortunately the overall mortality of sphincteroplasty and choledochoduodenostomy precludes their routine use and careful selection must be made.

Preoperative Evaluation

The value of an accurate history, elevated amylase, bilirubin, bromsulphalein, and alkaline phosphatase levels are well known. However, the role of the intravenous cholangiogram and morphine-prostigmine tests merits some discussion.

The intravenous cholangiogram is helpful in both primary and secondary cases.[49] The size of the bile duct is important since larger bile ducts are more likely to show pathology.[11,21] Ten millimeters, as measured by x-ray, is about the upper limits of normal and 14 mm is definitely dilated.[39,41] Care must be taken in correlating this to the actual size of the common duct to allow for magnification, distortion, and realization that this is the internal, not external diameter of the duct. Since it is now known that in man the common duct does not normally dilate after cholecystectomy,[9,23,45] serial observations showing an enlarging common duct indicate a partial obstruction at the ampulla. Conversely in evaluating a patient for pain following cholecystectomy, a small common duct that is unchanged in size is unlikely to be the cause of the patient's complaints. An occasional patient with biliary obstruction will not have a dilated duct because fibrosis and scarring of the thickened wall prohibit it. Partial obstruction of the distal bile duct can also be shown on the intravenous cholangiogram by loss of the normal tapering just above the papilla, followed by increasing opacification and dilatation of the hepatic radicles. In patients without a gallbladder, the time-density retention concept occasionally can be helpful to diagnose delayed drainage of dye into the duodenum.[49]

The morphine-prostigmine evocative test has been useful to screen patients.[31] After 10 mg of morphine and 1.0 mg of prostigmine, marked elevation of amylase or lipase levels, along with reproduction of the patient's pain, constitutes a positive test of pancreatic outflow obstruction. A positive test alone should not be a strong indication for surgery. It can be helpful when considered with the other evidence. In evaluating a positive test, reproduction of the patient's pain is as important as the elevated enzyme levels.

Operative Evaluation

The final decision for either a sphincteroplasty or choledochoduodenostomy is made at surgery and several operative findings are helpful.

Although occasional small bile ducts will have pathology, the chances increase markedly in bile ducts over 9 mm or 10 mm in diameter. Whenever possible the bile duct diameter has been measured directly with a small angled ruler between the cystic duct and duodenum before any cholangiogram is done (Fig. 1). Using this method the usual diameter of normal bile ducts not explored varied from 7 mm to 10 mm. Calipers or comparison to graded dilators can also be used but an accurate method of measurement is important.[21]

Routine cystic duct operative cholangiograms will outline the anatomy and pathology of the biliary tree.[46] The method has been described many times. If an initial film is taken after the injection of 2 or 3 cc of

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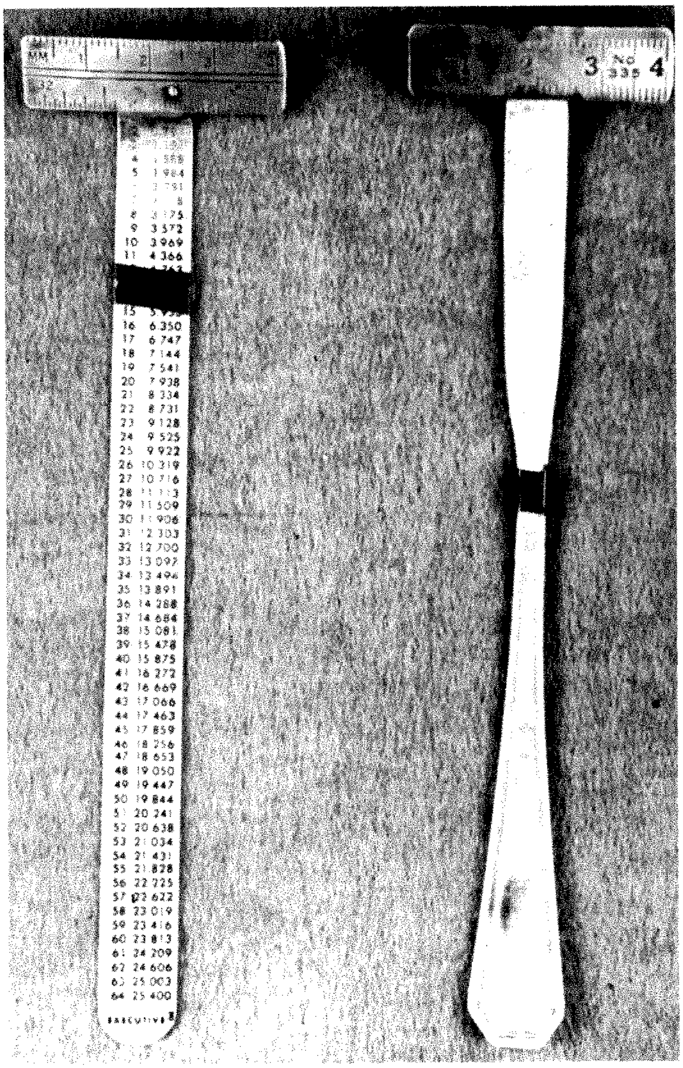


FIG. 1. Homemade rulers used to measure the width of the common duct, length of a sphincteroplasty, or diameter of a choledochoduodenostomy.

dye the distal bile duct and ampulla can be clearly seen. Absence of dye in the duodenum on this first film is strongly suggestive of partial biliary obstruction. Later films will give more information about the number and location of calculi. The possibility of spasm of the sphincter of Oddi due to fentanyl, narcotic analogues, and pressure injection should be remembered when interpreting the cholangiograms.[6]

The information gained from bile duct measurement and operative cholangiograms is helpful before the bile duct is explored.[30] The knowledge gained about the stones found in the bile duct is even more useful.[24] The presence of primary bile duct stones, thick bile or sludge, and hepatic calculi are all considered indications for one of the biliary drainage procedures. More controversial is the presence of multiple common duct stones that have come from the gallbladder. If the surgeon is convinced that the stones are all removed, if the ampulla dilates easily, and a completion cholangiogram is normal, an added procedure to drain the bile duct should be unnecessary. If he cannot be sure of these points, he should add a sphincteroplasty or choledochoduodenostomy. One of the drainage procedures should be performed at an operation for residual stones since the incidence of overlooked calculi in this situation is about 25%.

Evaluation of any ampullary stenosis is also important in deciding on a biliary drainage operation whether or not stones are present in the bile duct. Inability to pass a #10 French catheter or a #3 or occasionally a #4 Bakes dilator through the papilla has usually been an indication for a sphincteroplasty or choledochoduodenostomy unless the ampulla dilated easily under direct vision once the duodenum was opened.

Passage of dilators is only a subjective guide of ampullary stenosis since this will vary widely among surgeons. More objective evidence can be gained by manometric studies[47] and choledochoscopy.[37,38] Neither of these procedures has been used in this series. Both show promise for the future as they become more practical for widespread use.

The decision for a biliary drainage operation frequently is the result of a combination of the above preoperative and operative factors. Failure of passage of dilators when accompanied by a large bile duct, elevated alkaline phosphatase, or biliary sludge would indicate a drainage operation. Failure of passage of dilators in a normal sized duct with clear bile might only imply spasm of the sphincter and a biliary drainage procedure would be unnecessary.

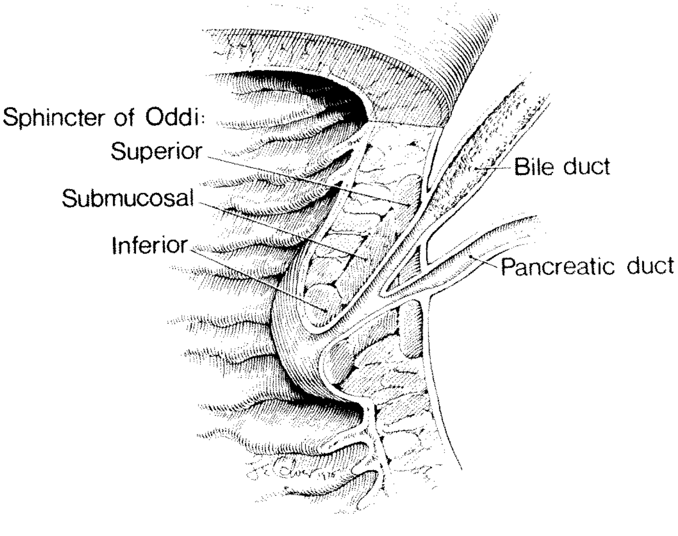


FIG. 2. Anatomy of the sphincter of Oddi showing the three parts described by Boyden.

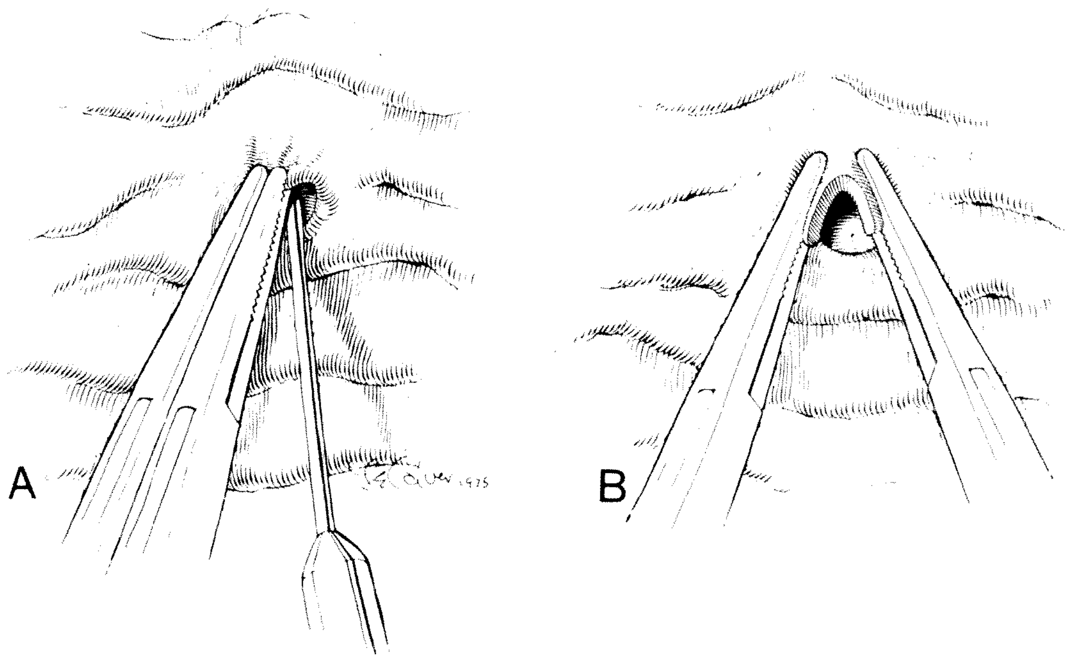


FIG. 3a and b. Operative technique of sphincteroplasty. a) First set of mosquito snaps is slightly lateral to avoid pancreatic duct. Dilator in duct is a guide to intramural path of bile duct. b) Sphincteroplasty incision started. Note pancreatic duct opening on the back wall.

Sphincteroplasty

In 1891 McBurney performed the first successful sphincterotomy to remove a bile duct stone.[28,29] Short sphincterotomy incisions were subsequently used to treat pancreatitis and retained stones, but were unsuccessful because they did not divide the complete sphincteric mechanism. Boyden pointed out that the sphincter is made up of three parts.[4] The important submucosal portion surrounds the bile and pancreatic ducts in their oblique course through the duodenal wall. Superiorly this blends with the duodenal muscle to form the superior sphincter. Inferiorly in the papilla it thickens to form the circular inferior sphincter (Fig. 2). The complete sphincteric mechanism surrounds the entire intramural length of the bile duct and may contract separately or together with the duodenal muscle. The length of this intramural portion varies from about 10 mm to 30 mm depending on the obliquity of the ducts. Jones, who developed sphincteroplasty in 1951,[17] emphasizes that the complete sphincteric mechanism must be divided to be permanently effective and the incision must extend through the entire thickness of the duodenal wall. His excellent results over 20 years have shown the need to do this and the value of his procedure as compared to a sphincterotomy.[18-20]

Method

Although others have done this operation without opening the supraduodenal portion of the bile duct,[13,50] these patients have had the bile duct opened first for exploration and aid in localizing the papilla. The duodenum and head of the pancreas are widely mobilized and then a short vertical duodenal incision is made over the papilla. A small dilator is passed from the bile duct into the duodenum to protect the pancreatic duct orifice and identify the intramural course of the bile duct. The sphincteroplasty is then performed by the serial application of straight mosquito snaps on the anterior common duct and posterior duodenal wall to completely divide the sphincter. The first pair of snaps is slightly lateral to avoid the pancreatic duct. The subsequent ones are directly anterior to be sure to stay on the common wall. The pancreatic duct is calibrated and avoided. The mucosa of the bile duct and duodenum are carefully approximated with interrupted 5-0 silk.

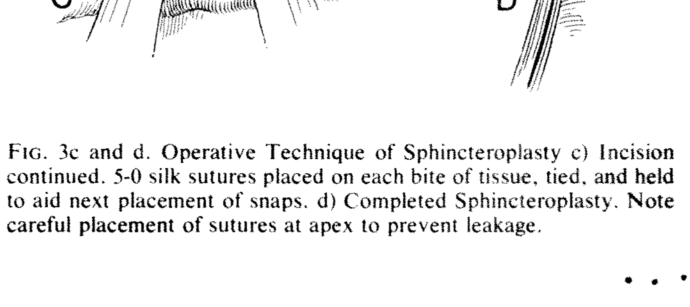
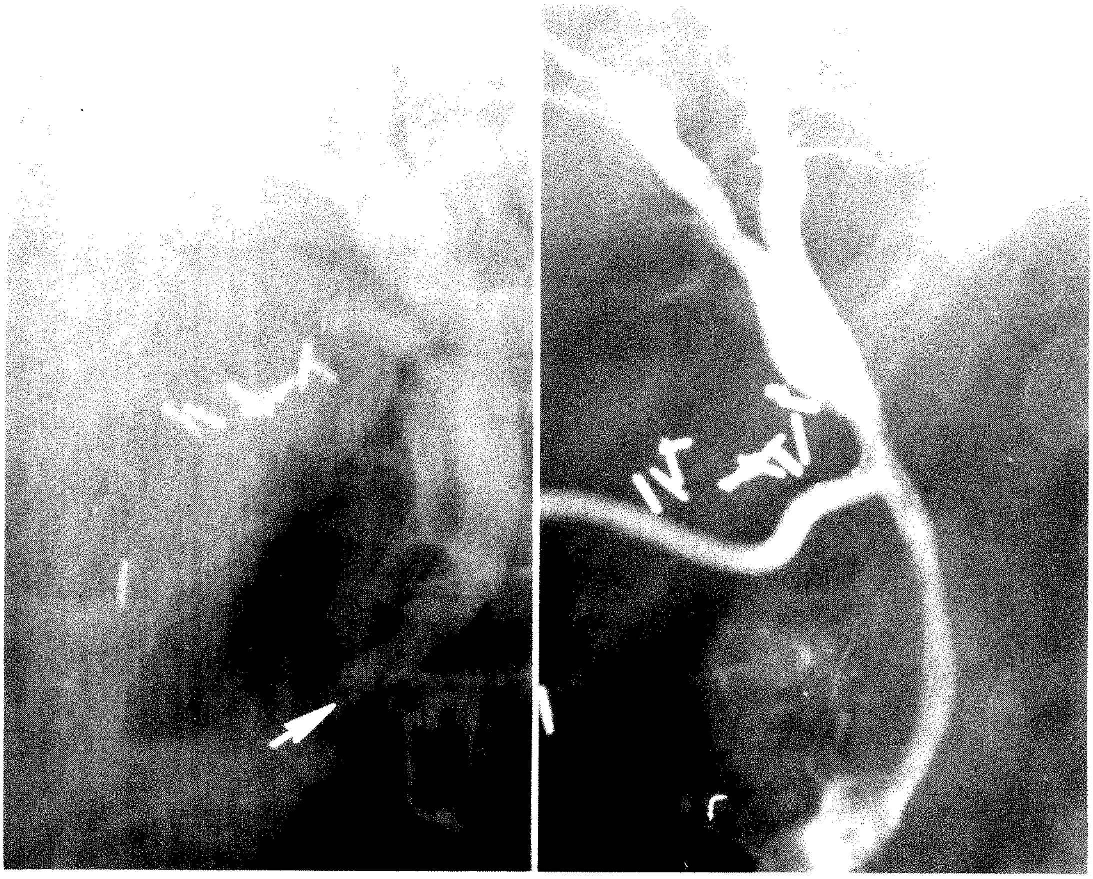


FIG. 3c and d. Operative Technique of Sphincteroplasty c) Incision continued. 5-0 silk sutures placed on each bite of tissue, tied, and held to aid next placement of snaps. d) Completed Sphincteroplasty. Note careful placement of sutures at apex to prevent leakage.



FIGS. 4a and b. (left) A cystic duct cholangiogram with arrow pointing to stone in ampulla. Duct is slightly enlarged and no dye goes into the duodenum. (right) A postoperative T tube cholangiogram showing a normal sized bile duct and wide open sphincteroplasty.

The division is continued until the diameter reaches that of the largest dilator that will fit in the bile duct. The entire sphincter mechanism is divided. Usually the incision will be 2.0 to 3.0 cm long but will vary with the intramural length of the bile duct. Meticulous suturing of the bile duct and the duodenum at the apex of the incision is essential to prevent leakage (Fig. 3).

It is difficult to know where to stop the incision. Unnecessarily long incisions are more likely to cause pancreatic injuries. Beattie, through autopsy studies, feels that the proximal end of the superior sphincter can be identified accurately by an abrupt change in the color of the mucosa from pink duodenal to the yellow honeycombed common duct mucosa.[3] This mucosal change can frequently be seen but has not been routinely used as a guide.

The duodenum is closed longitudinally in layers, the gallbladder, if still present, is removed and completion cholangiograms done to be certain about leakage. Because of the likelihood of bactibilia, prophylactic antibiotics begun preoperatively have been used routinely.[36] The operative area is drained and a short arm T tube is left in the bile duct for 2 to 3 weeks. Sphincteric biopsies have not been done unless a malignancy is suspected.

Results

Sixty of these patients have had a transduodenal sphincteroplasty. Fifty-two were primary procedures and 8 were secondary. Forty-seven were females and 13 were males. There has been no operative mortality.

The mean age of the primary group was 55 years and the average followup is 3.5 years. The main indications for the procedure were stones in the lower end of the duct requiring duodenotomy in 20 patients (Fig. 4), failure of passage of #3 or #4 Bakes dilators in 18, primary stones or sludge in 10 and multiple secondary stones in 4. The patients in whom dilators would not pass usually also had a large bile duct, abnormal operative cholangiogram, or elevated alkaline phosphatase to indicate partial biliary obstruction. Three of them had a positive morphine-prostigmine test. The bile ducts varied from 10 mm to 25 mm with an average diameter of 14 mm. Sixty-two per cent of these patients had stones in the bile duct at surgery. Many patients had a transient hyperamylasemia but only two had a pancreatitis that prolonged their hospital stay about 7 days. There has been no duodenal or pancreatic fistula.

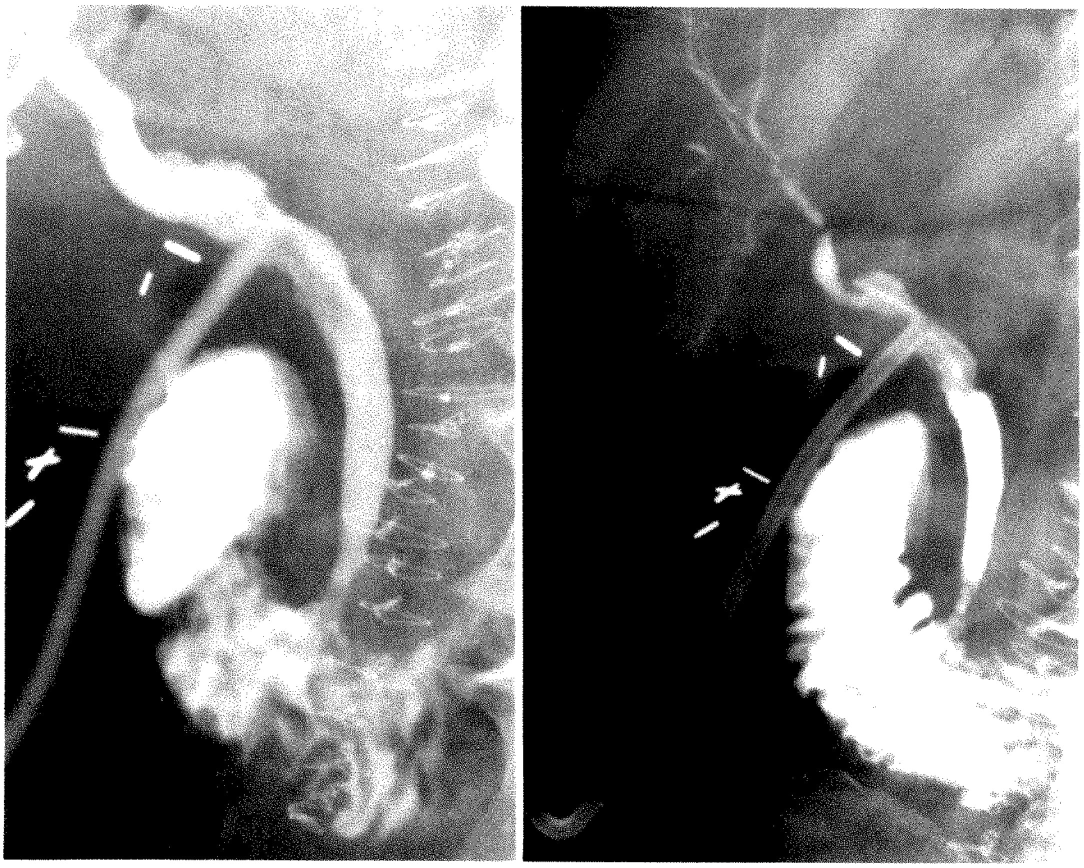
In long-term followup of the primary cases there have been 5 late unrelated deaths. None of these was connected to the bile duct problem. Forty-nine of these 52 patients can be classified as good or excellent results (Fig. 5). None of these has had any recurrence of jaundice, pain, cholangitis or had any subsequent hospitalization or operation related to the biliary tree. Three patients continue to complain of varying degrees of abdominal pain and have been hospitalized but do not have any objective evidence of bile duct problems. These three all had positive morphine-prostigmine tests preoperatively as their main indication for surgery. Their tests are now negative and gastrointestinal x-rays all show free reflux into the bile duct. None has had further surgery.

Eight patients had their sphincteroplasty as a secondary procedure an average of 17 years after their original operation. The mean age was 57 years and the followup averages 2.6 years. All of these 8 patients had pain like their original gallbladder pain. Seven of them had intravenous cholangiograms and in each the duct was 14 mm or greater in diameter. In one patient the duct enlarged more than 4 mm on serial examinations over a 2 year period. Morphine-prostigmine tests were done on 4 patients, being positive in 3 and negative in one. Only one patient was jaundiced. At surgery the bile ducts varied between 13 mm and 18 mm with an average diameter of 15 mm. Three of the patients had an associated cystic duct stump and only two had stones in the bile duct. A #3 Bakes dilator passed the sphincter on three of these patients, but a #4 failed to pass on all 8 of them. There were no significant postoperative complications.

In followup of the secondary group 6 of the 8 are symptom free with no problems. The remaining 2 still have abdominal pain. Their morphine-prostigmine tests are no longer positive and the gastrointestinal series shows reflux into the bile duct. Both patients have been rehospitalized but neither has had further surgery (Fig. 6).

Choledochoduodenostomy

In 1891 Sprengel performed the first successful choledochoduodenostomy to remove common duct stones and decompress the bile duct.[42] Numerous successful reports by Sanders,[34] Capper,[5] Mallet-Guy,[27] Madden,[25] Hurwitz,[35] Hoerr,[14] Johnson[15] and Magarey[26] point out the safety and effectiveness of this procedure. There has been concern that these patients would develop cholangitis but it is now clear that any cholangitis comes from stasis, not reflux,[10,25] and that the prime



FIGS. 5a and b. Postoperative x-rays of a patient with a good result. (left) T tube cholangiogram showing wide open sphincteroplasty. (right) G. I. series one day later showing reflux of barium into the bile duct.

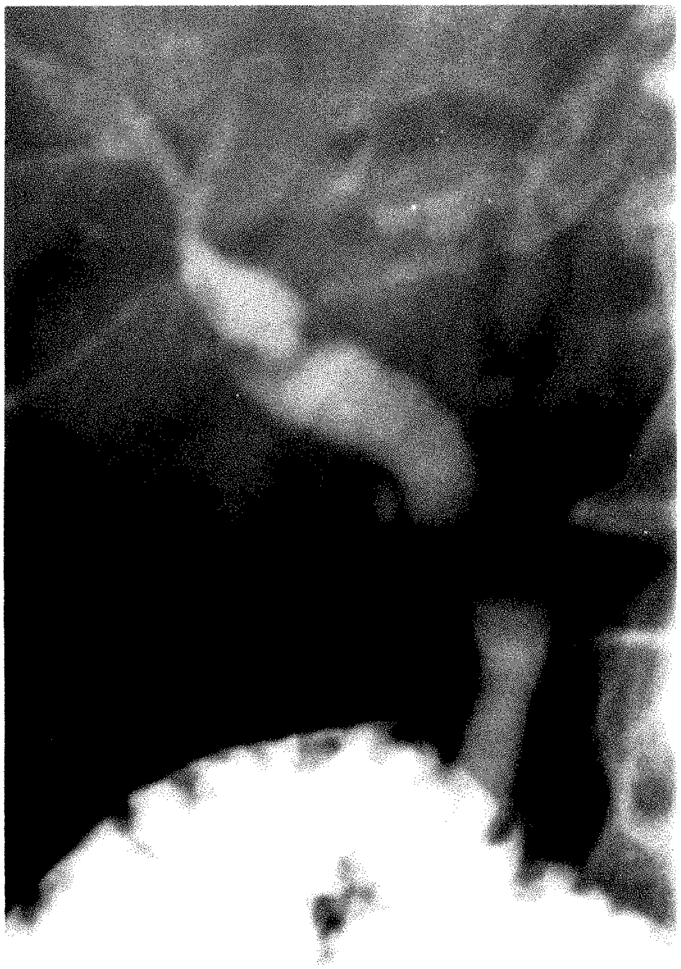


FIG. 6. A two year postoperative G.I. series on a patient who still has pain. X-ray shows free reflux of barium and air into the bile duct.

consideration in these cases is a large anastomosis at least 2.5 cm in diameter.[16] This is a surgical measurement. Postoperative transduodenal cholangiography by Ham and Sorby shows that many asymptomatic stomas are actually smaller than this.[12] The other concern about choledochoduodenostomy is the "sump syndrome" due to retained vegetable matter or calculi in the blind end of the duct.[17] This does occur but must be relatively uncommon.

Method

Here the choledochoduodenostomy has been done with a longitudinal incision in both the bile duct and the duodenum. The incision in the bile duct is as distal as possible, and the incision in the duodenum is on the posterior wall excising an ellipse of mucosa.[7] A two-layer interrupted anastomosis has been used that measures at least 2.5 cm in diameter. A T tube, placed in the duct above the anastomosis with the lower arm going into the duodenum, is used for two to 3 weeks, and the operative area is drained (Fig. 7). Prophylactic antibiotics begun preoperatively have been used routinely. It is important to decide on this procedure before the duodenum is opened. Otherwise the duodenal and bile duct incisions may be improperly placed and a poor anastomosis with tension will result.

Results

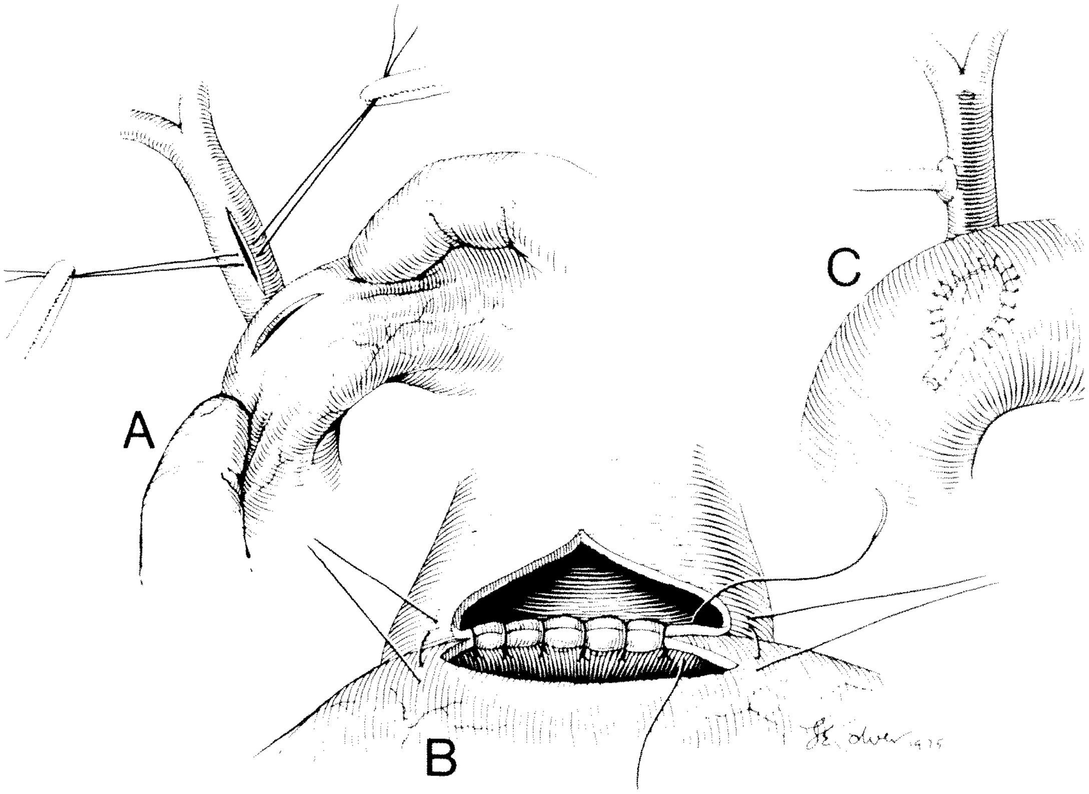
Thirteen patients in this series have had a choledochoduodenostomy. All have been as a primary procedure. Eight are female and five are males. There has been no operative mortality. The average age of these patients is 71 years. The followup has averaged 3 years. The main indication for biliary decompression was large primary stones or sludge in 7 patients, multiple stones in 3, and failure of passage of a #4 dilator in 3. Five of these patients had large periampullary diverticula and 4 others had an inflamed pancreas. The bile duct diameter varied from 16 mm to 30 mm with an average of 24 mm. All 13 patients had stones in the bile duct, and the lower end of the duct was cleared of stones and debris at surgery in all but one patient.

There have been no significant operative complications. There have been two late unrelated deaths. All but one of the patients are symptom free with no evidence of cholangitis (Fig. 8). None of the patients has had further hospitalizations related to any gastrointestinal symptoms. Nearly all of the patients have had subsequent upper gastrointestinal series and all show free reflux of barium into the biliary tree. One patient has had recurrent episodes of pain similar to his previous pain but no chills or fever. His alkaline phosphatase and bilirubin levels are normal. A gastrointestinal series shows free reflux and drainage but also a presumed calculus or debris in the distal bile duct although the duct had been cleared at surgery. So far symptoms have not warranted re-exploration but he probably is an example of the "sump syndrome" (Fig. 9).

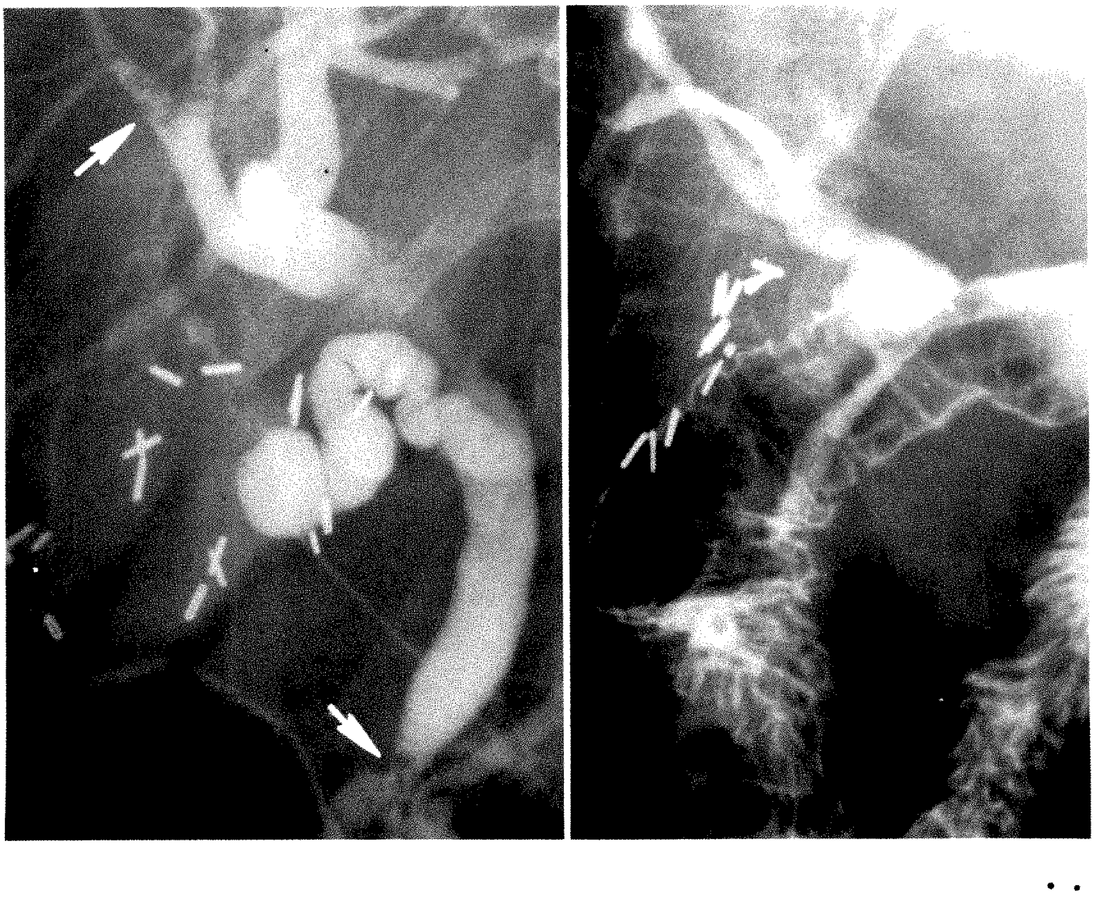
Discussion

Sphincteroplasty has been the preferred biliary drainage operation in this series of patients. A complete procedure dividing the entire sphincter is done to produce a permanent large opening. As shown by long followup the stomas stay open and do not constrict down.

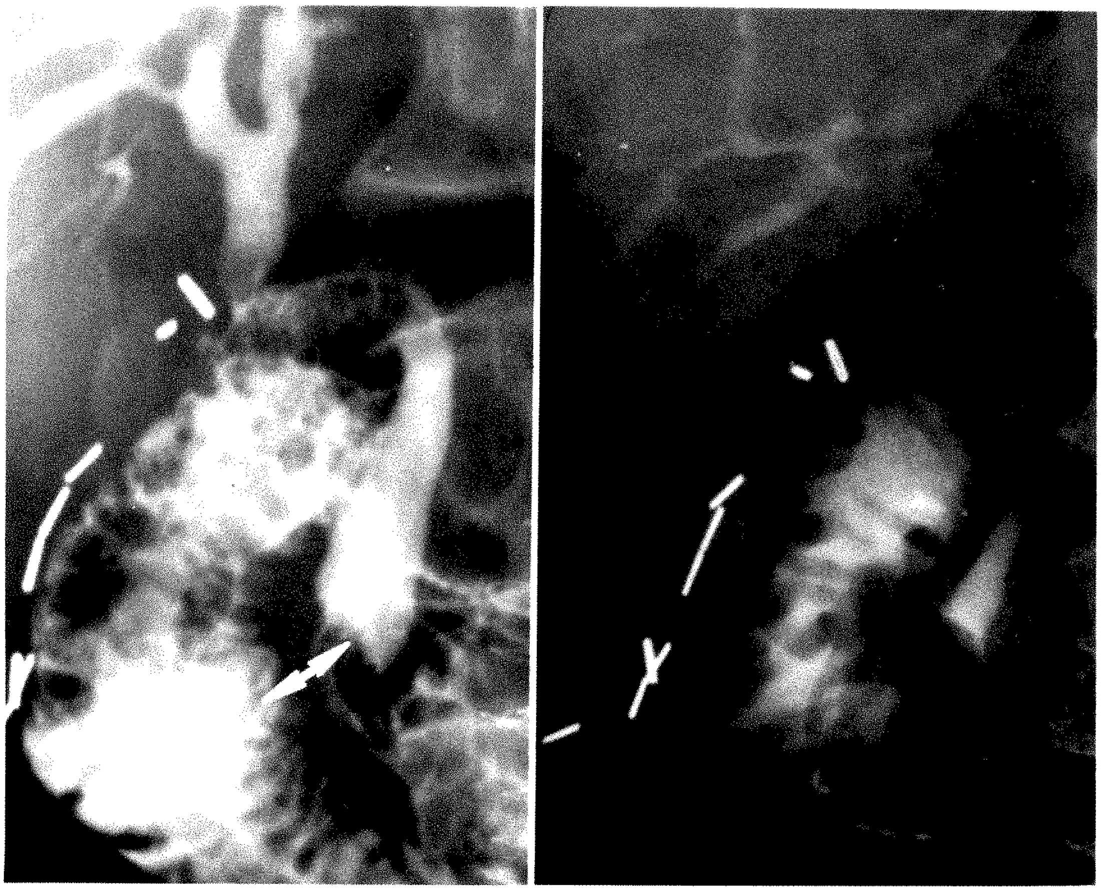
The particular advantages of a sphincteroplasty as compared to a choledochoduodenostomy are: dependent drainage of the bile duct, ease of removal of impacted



FIGS. 7a to c. Operative Technique of Choledochoduodenostomy. a) Incisions are on distal bile duct and back wall of duodenum to make a comfortable anastomosis without tension. b) Two layer interrupted anastomosis should measure at least 2.5 cm in diameter. c) Completed anastomosis with splinting T tube.



FIGS. 8a and b. Patient who had a choledochoduodenostomy because of multiple stones and an inflamed pancreas. On left an operative cystic duct cholangiogram. Arrows point to stones in ampulla and right hepatic duct. On right a two year postoperative G.I. series showing free reflux into bile duct and narrow segment of distal duct Patient is asymptomatic.



FIGS. 9a and b. Four year postoperative G.I. series on a patient with presumed sump syndrome. On left, note free reflux of barium into bile duct but lower end is bulbous and double arrow indicates terminal segment filled with a stone or debris. On right, a delayed film still outlines crescent-shaped defect in distal duct.

ampullary stones and debris, and good visualization of the papilla, pancreatic duct, and distal bile duct to insure that no pathology is overlooked. The greatest value of sphincteroplasty has been to prevent residual or recurrent bile duct stones and to relieve true ampullary stenosis.

The main disadvantage of a sphincteroplasty is that it requires more extensive manipulation of the pancreas and bile duct and should be avoided if significant active inflammation exists. Sphincteroplasty has a higher mortality and morbidity because of postoperative pancreatitis, cholangitis, and duodenal fistula. This is partly due to operative trauma, but is also due to bactibilia secondary to stasis in the bile duct.[14] Further, sphincteroplasty will not be satisfactory for occasional long strictures of the distal bile duct nor will it adequately drain a huge bile duct.[22]

Choledochoduodenostomy has also given good results. Its particular advantages compared to sphincteroplasty include requiring less manipulation of the pancreas and bile ducts. It is a simpler operation and will be more suitable for the obese, elderly or poor risk patient who has severe inflammation or multiple diverticula around the ampulla. It more adequately drains a huge bile duct and could be used for unusually long strictures of the distal duct.

Choledochoduodenostomy also has several disadvantages. It is a blind procedure and pathology in the ampullary area can be overlooked. A cul de sac is left in the distal bile duct where retained calculi or debris can become symptomatic or new stones can form. Further, the procedure is suitable for only those patients with large enough ducts to make a 2.5 cm diameter anastomosis with the duodenum.

Opinion of the frequency of the sump syndrome varies. Madden[25] has not seen it in his patients and Magarey[26] believes it is rare. Jones[17] regards it as a serious disadvantage and Smith has reoperated on at least 25 patients because of this debris.[17,40] His procedure has been to preserve the choledochoduodenostomy and add a sphincteroplasty to clean out and drain the blind distal duct.

Although the followup in these 73 patients is short, there have been minimal late gastrointestinal symptoms. None has developed any pancreatic or biliary malignancy and none has had any jaundice or subsequent stone problem. Five patients with a sphincteroplasty still have varying degrees of pain. In all of these a positive morphine-prostigmine test was a prime indication for surgery. This is actually more criticism of patient selection than the actual operation. One patient with a choledochoduodenostomy is presumed to have symptoms of a "sump syndrome" but has so far not had an exploration. All other patients with either the sphincteroplasty or the choledochoduodenostomy are symptom free.

The group of 102 private patients from the entire series with common duct exploration without a sphincteroplasty or choledochoduodenostomy has had a greater morbidity and mortality than those with the biliary drainage operations. One patient who had a transduodenal dilatation of the ampulla without sphincteroplasty died of postoperative pancreatitis and another has a retained asymptomatic common duct stone. One patient who had a supraduodenal duct exploration had a prolonged biliary fistula after removal of the tube and another has had to have a repeat choledocholithotomy. Several others have had to be readmitted for upper abdominal pains and personal followup on the rest brings out a higher incidence of upper gastrointestinal complaints.

This suggests that the addition of a sphincteroplasty or choledochoduodenostomy in complicated bile duct explorations does not necessarily add to the morbidity and mortality of the operative procedure. It does not mean that one should do routine sphincteroplasties or choledochoduodenostomies but does imply that these drainage procedures may actually be a safety factor. A patient who requires a duodenotomy to remove an ampullary calculus may have a lower chance of morbidity and mortality if a sphincteroplasty is added. As this series of patients has evolved, fewer bile ducts have been explored, but more of those with duct explorations have had a biliary drainage procedure, usually a sphincteroplasty.

Conclusions

Both transduodenal sphincteroplasty and choledochoduodenostomy have been valuable for benign biliary obstructions. Sphincteroplasty has been preferred because it gives dependent drainage, direct inspection of the ampullary area, and facilitates removal of impacted stones and debris. It is not always applicable, and choledochoduodenostomy has been chosen in elderly poor risk patients or those with pancreatic inflammation or periampullary duodenal diverticula. Both operations must be done carefully. Both have specific advantages and limitations such that the surgeon should not use one to the exclusion of the other.

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DISCUSSION

DR. CLAUDE E. WELCH (Boston): Dr. Rutledge followed these patients very closely. Furthermore, he has had extraordinarily good results. It therefore would be very hard to quarrel with his philosophy.

On the other hand, I think it must be admitted that if the same results can be acccomplished by one method that is simpler than another, perhaps that should be the better method to use.

He has had no mortality in his more extensive operations; yet I am sure that most of us in the audience, doing the same thing, would have more difficulty than he has had.

When I review my results and modify my techniques on the basis of my mistakes—and I think that's what most of us have to do—the fact stands out that stones are left in the common duct that cannot be detected by our ordinary methods of exploration, and therefore have to have recourse to one of these other methods that Dr. Rutledge has used.

I recommend the increased use of the choledochoscope, which in our hands has been very effective in identifying and removing stones not found by any other method. If this is done, I believe we will be able to increase the number of explorations done supraduodenally of the common duct, and reduce the number that will require the more extensive operations.

This is merely another philosophy, and Dr. Rutledge has something that is absolutely perfect in his hands. I don't think he has any reason to change, but perhaps the alternate could be used at times.

DR. COLIN G. THOMAS, JR. (Chapel Hill): We have been interested in both these procedures, and presented our findings before this society about five years ago. We agree that the most common indication for either of these operations is partial common duct obstruction which is associated with stasis and the development of bilirubinate stones or mud. Both operations appear to be effective.

The chief morbidity in our hands has been related to infection and pancreatitis. The former can be minimized by recognizing the high incidence of bactibilia in patients with partial common duct obstruction, and the latter, as emphasized by Dr. Rutledge, by avoiding manipulation or instrumentation of the common duct in the region of the pancreas.

Pancreatitis is less frequent after choledochoduodenostomy than with sphincterotomy. Dr. Rutledge has avoided this complication very nicely in both procedures.

In the appraisal of common duct obstruction by operative cholangiography, caution must be exercised in the interpretation of films when the patient is receiving narcotics or fentanyl citrate. This may give a false impression of obstruction due to spasm in the region of the sphincter. The anesthesiologist can frequently prevent this associated spasm by the judicious administration of atropine prior to the operative cholangiogram.

We have evaluated the need for sphincteroplasty or choledochoduodenostomy by measuring the opening pressures within the common duct by the use of manometry. With a normal opening pressure—that is, less than 18 cm of water—a duct of normal caliber, and in the absence of bilirubinate stones or mud, there is little indication for either of these operative procedures.

Theoretically, sphincteroplasty should be physiologically more sound than choledochoduodenostomy. However, in our earlier experience it was associated with a higher morbidity and mortality. Since our report five years ago a review of 100 patients undergoing cholecystectomy revealed that choledochoduodenostomy was the most common procedure performed for relieving common duct obstruction. In these 100 patients undergoing cholecystectomy, ten had an associated choledochoduodenostomy, and only one a sphincteroplasty. There was no mortality.

I should like to ask two questions. We have had no experience with the morphine-prostigmine test, and I'd like to ask Dr. Rutledge his indications.

Secondly, in view of his improved results in patients undergoing these procedures as compared with those patients that did not have the operation, does he advise a more liberal attitude toward their use in the future?

DR. PAUL C. KIERNAN (Washington, D.C.): My experience consists of only 12 cases, but it convinces me of the conclusions so well documented by Dr. John L. Madden, that remarkable surgeon and distinguished Fellow of this organization, that choledochoduodenostomy is a much maligned procedure.

Criticism has often centered upon cholangitis as a complication of the procedure. I do not believe this to be true. As Madden has detailed so well, cholangitis is a complication secondary to obstruction of the biliary decompression. Hence, his precise delineation of the problem of proper egress of bile, rather than reflux.

In 1882 Dr. Von Winiwater performed the first biliary-enteric anastomosis of the gallbladder to unprepared colon. Subsequently, and successfully, Drs. Arthur Mayo Robson, Chevasse, Courvoisier, performed cholecysto-colostomies.

Sphincterotomy and sphincteroplasty seem too susceptible to scarring, hindrance to proper bile egress; hence "descending cholangitis."

In the late 1950's Dr. Eiseman, in an experimental study, noted only seven weeks post-sphincterotomy scarification, and common duct pressures exceeded those noted at the original operation.

Other complications of sphincterotomy, or sphincteroplasty, are bleeding, pancreatitis, and fistula formation.

Quoting Dr. R. L. Sanders, "sphincterotomy is making an easy operation a difficult procedure."

Simplicity is best served by choledochoduodenostomy.

In Madden's 138 cases, only one instance of "descending cholangitis" occurred, that due to inadequate diameter of the anastomosis.

Dr. Sam E. Stephenson, Jr. (Jacksonville, Florida): Some years ago, Dr. Scott and I were interested in the transduodenal sphincteroplasties in patients with common duct problems, and continued this for some time. Because of the increased risk of postoperative pancreatitis, the recurrence of narrowing, in the last few years I have changed my mind.

(Slide) Over the last three years we have had the opportunity to treat 22 patients who needed decompression of the common duct. Thirteen of these were impacted stones, six constrictive pancreatitis, causing stricture formation with dilatation, one carcinoma of the pancreas, which I hesitated to do, but this patient lived a year and a half in a nursing home, dying of a myocardial infarction with a patent opening, one for sclerosing cholangitis which is only nine months postop, but has been asymptomatic since that, and then a new indication which has not previously been called upon for choledochoduodenostomy, that of a patient with bile peritonitis secondary to a rather ignominious common duct exploration by a pediatric surgeon.

(Slide) Our duct sizes, irrespective of the literature—that 12-year-old who had been operated because she was a sickler with stones, who had a history of jaundice, with no preoperative cholangiogram, had the 8 mm common duct opened, with no T-tube small enough to fit it in, four days postoperatively developed signs of bile peritonitis. On reexploration I could find no way to repair the duct short of a choledochoduodenostomy.

She lived four and a half years, to die of a further complication of her sickling disease, with a patent anastomosis.

There were no operative deaths. There was one subhepatic abscess requiring drainage. There was no recurrent jaundice. There was no ascending cholangitis. And there was no post-op pancreatitis. Suffice it to say that at the current time this is our procedure of choice.

Dr. J. Philip Sandblom (Lausanne, Switzerland): Mr. President, please excuse me for rising twice, but I thought it was my duty, as I belong to those who maligned the procedure of choledochoduodenostomy, and the reason is this.

I want to congratulate the author, because it's remarkable, with the little frequency of postoperative cholangitis, just the same as in Dr. Madden's experience. And this is different from only about ten or 15 years ago, when, if you followed those series long enough, and more than five years, they will always in about 20% have periods of assending cholangitis with frank symptoms.

We have to follow those patients for more than five years, because it takes some time before the anastomosis shrinks enough to give frank cholangitis. I think it is due to the fact that the modern surgeons will do better anastomoses, which stay open better. It is also a fact that if you go through large materials of operations for biliary structures, two thirds of the patients will have been operated on twice, or more times, for continued stricture of the anastomosis.

Another thing is that even if you don't have frank cholangitis, with shivers and jaundice, you might have cholangitis anyway. It's hard to diagnose.

For this reason I went through about ten years ago all the cases I could find that had autopsy more than five years after a biliodigestive shunt. In about 20, four had had frank cholangitis, with chills and fever, and many had multiple small, miliary abscesses.

This is one of the reasons why we think that the biliodigestive shunt, whether choledochoduodenostomy or sphincteroplasty, should be done with some hesitation, and with strict indications. It is surprising to see the difference in frequency of doing biliodigestive shunts in operations for common duct stones. Here I think they ought to have had about 50% of such procedures for common duct stones. In our material, which is very large, we generally have about three or four cases of biliary cases every day in Lund, and in only about 2% of cases of common duct stones will we have to do biliodigestive shunts.

This is due to the fact that we pay such an attention to the preoperative cholangiogram. This should be done before any other procedure, without air, with injection only of 2 or 3 cc at the first injection, and with photography in at least two projections. With perfect cholangiograms the rick of retained stones is small, but, naturally, we have them, as everybody; but we are very restrictive with the biliodigestive shunts.

Dr. William P. J. Peete (Durham, North Carolina): I have a hundred or more patients of this nature. There must be some difference between North Carolina and Texas, because, as Dr. Sandblom, we have not had to do sphincteroplasty or choledochoduodenal anastomosis nearly so frequently.

Since neither he nor many of our other colleagues have had many complications with choledochoduodenal anastomosis, I'd like to tell you how to get out of trouble, in case you get into it. In about 700 patients who have had to have operations of this nature, we have done 22 choledocal anastomoses. One was reported here in connection with common duct structure discussion, beginning 25 years after Dr. Charles Lux the Senior had done the original anastomosis.

In two others that I have done at Duke, at reexploration for ascending cholangitis, in distinction with Professor Sandblom's patients, all of these anastomoses were widely patent, and I think they were having an ascending cholangitis, perhaps in part becuase they no longer had the proper amount of acid in their stomach. At any rate, division, distal to the pylorus, antrectomy, and vagotomy in two resulted in complete cessation of symptoms.

The third patient had a dilated common duct, had dilated hepatic radicles, and continued to form stones, which intermittently spit through the new anastomosis for a period of a year or so. These situations were relieved by antibiotics, and eventually we placed this patient on chronic tetracycline antibiotic therapy. He's not been seen for two years; we know, though, he is doing well.

Dr. Robb H. Rutledge (Closing discussion): First, I want to thank Dr. Welch for his kind remarks. I have not used a choledochoscope in these patients but agree with him that it has real value in evaluating the bile duct. I look forward to using it in the future.

Dr. Thomas, thank you for your remarks. Your point about spasm in the operative cholangiograms is very important. I have mentioned it in the manuscript and agree that it must be kept in mind when interpreting the films. I have not used manometry. Dr. T. T. White in Seattle has had extensive experience with this. When more practical equipment for routine use becomes available, I should probably add it to the operative procedure. Dr. Thomas, I use the morphine-prostigmine test frequently but am not totally sold on it. Dr. Nardi and Dr. Bartlett in Boston have used it a great deal. The patients in both my primary and secondary groups who have had poor results with persistent pain had a positive morphine-prostigmine test as their main indication for surgery. Three patients in the primary group had poorly functioning gallbladder x-rays without stones but markedly positive morphine-prostigmine tests. They continue to have pain like before but their tests are now negative. Taken in conjunction with an elevated alkaline phosphatase or a large bile duct on an intravenous cholangiogram the positive test is helpful. It is not reliable as the sole indication for surgery. Dr. Thomas, I can't answer whether or not we should do this type of surgery more liberally. I probably do it more frequently than many surgeons do.

Dr. Kiernan, I thank you for your remarks. In my opinion the main danger of a choledochoduodenostomy is not cholangitis but is a sump syndrome. I know Dr. Madden feels he does not see it but Mr. Rodney Smith in England has operated on over 25 patients with a sump syndrome who had impacted vegetable debris in the bottom of the bile duct. Dr. Kiernan, you mentioned Dr. Eiseman's work with pressure studies after a sphincterotomy. This divides only the inferior sphincter and is not what I am doing. Dr. Austin Jones has emphasized that you have to divide all three parts of the muscle in a sphincteroplasty. A short sphincterotomy dividing the inferior muscle cannot be equated with a sphincteroplasty.

I want to thank Drs. Stephenson, Sandblom, and Peete for their comments. I will disagree with my friend, Billy Peete, on one thing. He feels we have more tight sphincters in Texas than they do in North Carolina. Chapel Hill is about 15 miles down the road from Durham. Dr. Thomas mentioned that in their last 100 cholecystectomies they did 10 choledochoduodenostomies and 1 sphincteroplasty. That is 11%. In my patients these operations made up 12% of the entire series. That's pretty close. Thank you all very much.

Long Term Transhepatic Intubation for Hilar Hepatic Duct Strictures

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A technique for repairing benign high hilar hepatic duct strictures using transhepatic intubation with a large bore silastic stent is described. This procedure has been used in 10 patients. In 9 instances the stricture involved the common hepatic duct, and in one patient the right and left hepatic ducts. Nine of the strictures followed cholecystectomy; one followed the primary repair of a gun shot wound to the hepatic duct. Hepaticojejunostomies were created and the transhepatic silastic stent was left in place for 6 months in one patient, and for 12 months in 8 patients. In one patient the silastic stents are still in place. There have been no treatment failures. All patients are healthy and at full activity from one year, 3 months to 6 years, 6 months from the time of repair (average 3 years, 5 months). In the 9 patients whose stents have been removed, the serum bilirubin levels are normal. There have been no episodes of cholangitis following repair. This method of repair using long term transhepatic silastic stents is recommended for all high hilar hepatic duct strictures.

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BENIGN STRICTURES of the biliary tree continue to present a formidable surgical challenge. Repairs are difficult, the need for reoperation common, and long term results often disappointing. Particularly challenging are those strictures that occur high in the hepatic duct in the hilum of the liver. Identification of the ductal system at operation can be difficult, and because a satisfactory proximal biliary segment is often absent, a mucosa to mucosa anastomosis may be impossible. Over the past 7 years 10 patients with high hilar hepatic duct strictures have been treated at The Johns Hopkins Hospital. The surgical technique using transhepatic intubation with a large silastic stent and long term results in these 10 patients are presented.

Clinical Material

Between 1969 and 1974 10 patients, with high hepatic duct strictures were treated at The Johns Hopkins Hospital (Table 1). In 9 instances the stricture involved the common hepatic duct, and in one instance (Patient S.D.) both the right and left hepatic ducts were involved. Ages ranged from 19 years to 68 years, and averaged 36 years. Eight were women, and two were men. Seven patients were Caucasian and three were Negro. In 9 patients the stricture resulted from an injury at the time of cholecystectomy. Two of these 9 patients had undergone one prior attempt at repair, and one patient had undergone two prior repairs. In the tenth patient, the bile duct was transected by a gun shot wound. A primary end to end anastomosis was carried out, which subsequently strictured.

The interval between cholecystectomy and the development of jaundice in the 6 patients who had no prior attempt at repair varied from 2 weeks to 7 months. The interval between stricture repair and the development of jaundice in those 4 patients who had previously undergone an attempt at repair varied from 4 months to 29 months. At the time of admission for stricture repair the serum bilirubin varied in these 10 patients from 2.1 mg% to 19.3 mg%, and averaged 8.4 mg%.

Treatment

Prior to operation the anatomy of the biliary tree was defined by percutaneous transhepatic cholangiography in 5 patients (Fig. 1). Two patients had indwelling T tubes following previous repairs, and satisfactory definition of the stricture was obtained by T tube cholangiography. In one patient with an external biliary fistula, injection of the sinus tract resulted in satisfactory visualization of the bile ducts. In the last two patients cholangiography was performed intraoperatively at the time of repair.

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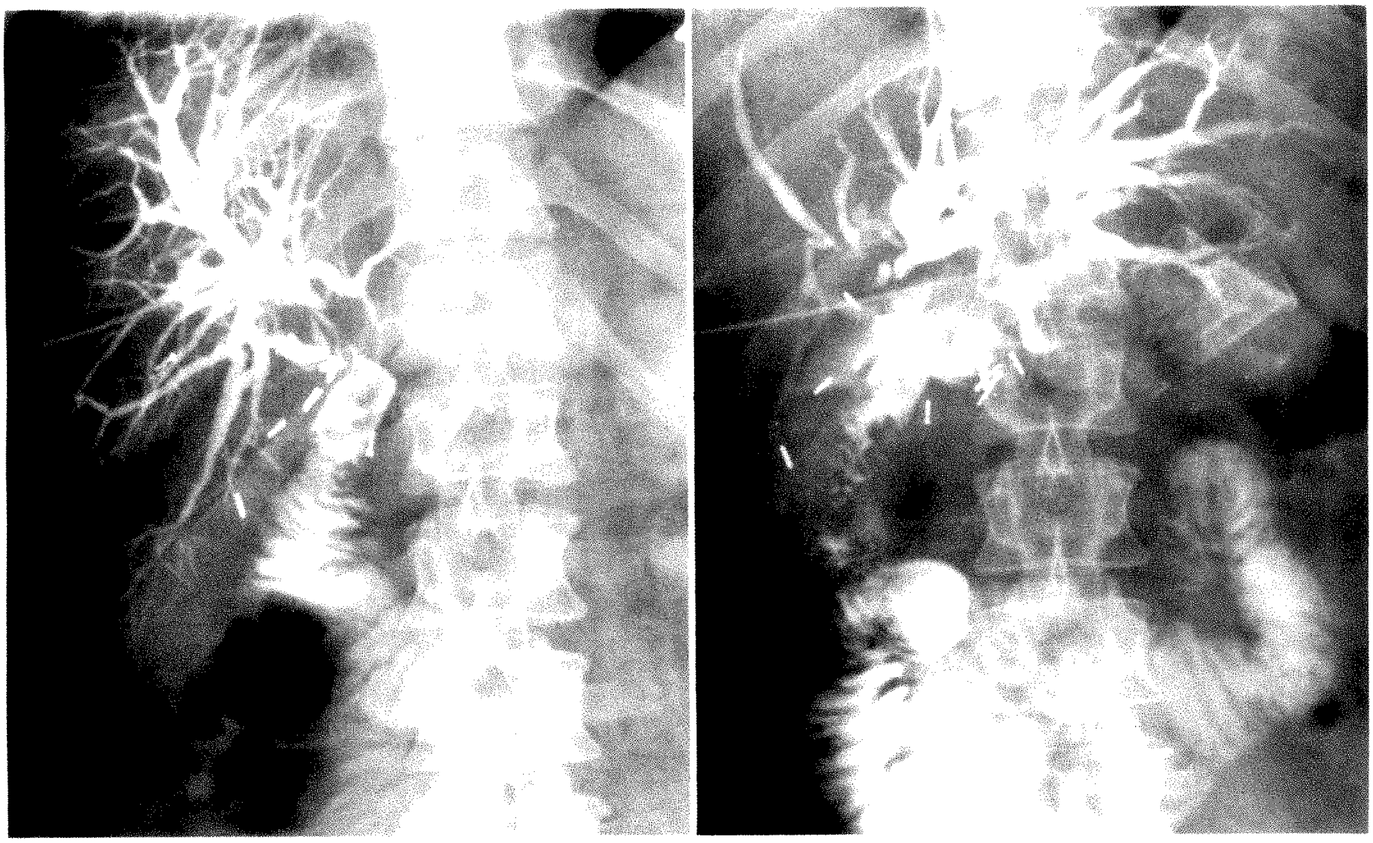
TABLE 1. *Ten Patients With Hilar Hepatic Duct Strictures*

Patient	Age, Race,* Sex	Etiology	Prior Repair	Admission Bilirubin mg%
E.N. #41 66 10	34, N, F	Surg Trauma	one	7.1
R.G. #148 65 12	68, C, M	Surg Trauma	no	2.8
L.T. #152 19 43	19, N, F	Surg Trauma	no	3.9
S.D. #155 99 49	50, C, F	Surg Trauma	two	7.7
J.B. #137 70 54	24, C, F	Surg Trauma	one	17.4
A.V. #147 37 55	35, C, F	Surg Trauma	no	12.8
T.W. #131 40 59	19, N, M	Gun Shot Wound	one	4.0
B.T. #146 37 65	29, C, F	Surg Trauma	no	2.1
J.L. #144 53 90	36, C, F	Surg Trauma	no	6.9
G.S. #143 20 94	43, C, F	Surg Trauma	no	19.3

* C—Caucasian; N—Negro.

Surgical repair involved identification and dissection of a proximal hepatic duct remnant. In each instance this was found high in the hilum of the liver, often within the liver parenchyma (Fig. 2). In no instance was a segment of normal proximal duct obtained that would allow a mucosa to mucosa anastomosis. Once the biliary tree was identified, an acutely curved Randall stone forceps was placed into the intraparenchymal hepatic duct, usually the right, and advanced superiorly and anteriorly into the anterior segmental duct until it approached within 1 cm of Glisson's capsule. At this point the liver was incised with a scalpel and the tip of the stone forceps extended through the surface (Fig. 3). A silastic stent 60 cm in length and 1 cm in outside diameter was tied to the end of the stone forceps. Multiple holes had been placed in the silastic tube throughout half its length (Fig. 4), and the end containing the holes was drawn down through the liver and out the hilum. The opposite end of the stent, protruding from the anterior superior surface of the right lobe of the liver, was brought out through a stab wound in the right upper quadrant onto the anterior abdominal wall. A Roux-en-Y jejunal loop was then constructed



FIGS. 1a and b. Preoperative percutaneous transhepatic cholangiogram. This study required inserting the cholangiogram needle first into the right hepatic duct (a), and then into the left hepatic duct (b) to visualize the entire biliary tree. The patient (S.D.) had a stricture at the bifurcation and the right and left ducts did not communicate. Having this information prior to surgery was of great importance.

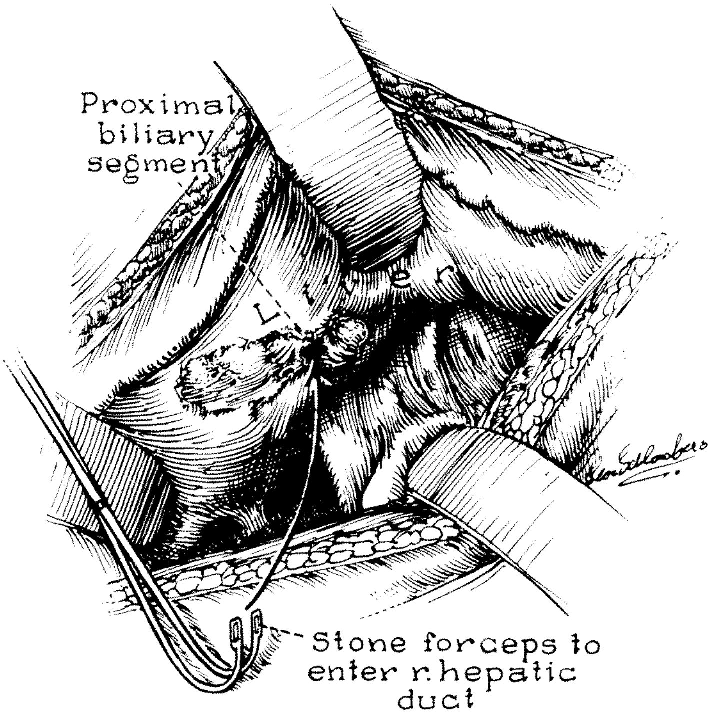


FIG. 2. The bifurcation of the hepatic duct has been identified as it enters liver parenchyma. Good mucosa generally is not present circumferentially in these high strictures. For passage of the transhepatic stent, acutely curved stone forceps are used.

and placed in the hilum of the liver (Fig. 5). The silastic stent was introduced into the side of the Roux-en-Y loop through a stab wound. The side of the jejunal loop was then sutured to the hilum of the liver using one or two layers of non-absorbable suture material. The hepaticojejunostomy was carried out using full thickness of the jejunum, and hepatic duct, liver capsule, or any other tissue available in the hilum. Two Penrose drains were left in the area of the anastomosis, and two additional drains were left in the area where the silastic stent penetrated through the anterior superior surface of the liver. In the patient with strictures of both the right and left hepatic ducts, a silastic stent was placed in the main left hepatic duct. The main right hepatic duct could not be identified. What probably was the anterior segmental branch of the right hepatic duct was identified and cannulated with a second silastic stent. Operative time varied from 4 hours and 15 minutes to 10 hours and 15 minutes, and averaged just over 7 hours. Most of the operative time was spent in locating and dissecting out the proximal biliary segment. Once the biliary tree was located, insertion of the transhepatic stent and anastomosis of the Roux-en-Y proceeded rapidly.

Following surgery the silastic tube was left open and connected to a bile bag. When a postoperative cholangiogram revealed the anastomosis to be healed, the silastic tube was clamped. Once a day thereafter until the stent was removed the tube was irrigated with 20 ml of saline. In one patient with silastic tube was removed 6 months following repair; in 8 patients the tubes were left in place for 1 year. In the one patient with silastic stents in both the left and right hepatic ducts, the stents remain in place 15 months following repair. In several patients the silastic stents were replaced during the year following surgery when they became partially occluded with biliary sludge. This was performed in the outpatient clinic under fluoroscopic control by first passing a guide wire down the lumen of the silastic stent into the Roux-en-Y jejunal loop. The stent was then removed leaving the guide wire in place. The new tube was then easily slipped in place over the guide wire (Fig. 6).

Results

All 10 patients developed biliary cutaneous fistulas following surgery. In each patient bile leaked for several days from the surface of the liver at the exit site of the silastic stent. In addition, most patients initially leaked a small amount of bile from the site of the hepaticojejunostomy. In all 10 patients the transhepatic silastic stent was left to dependent drainage until bile drainage along the Penrose drains ceased, and a transhepatic tube cholangiogram revealed the biliary tree to be sealed. All biliary fistulas closed with 3 weeks. Two patients developed a subhepatic abscess following repair and re-

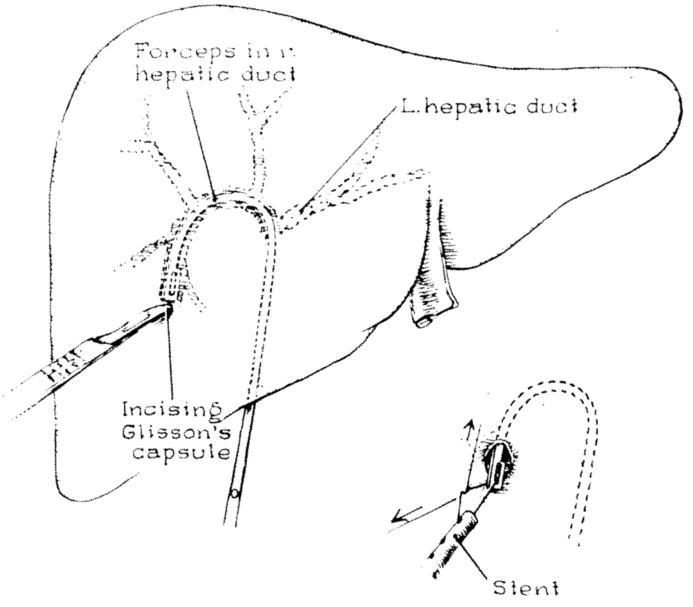


FIG. 3. The acutely curved Randall stone forceps are passed into the anterior segment of the right hepatic duct and can be brought to within one or two centimeters of Glisson's capsule. The capsule is then incised, the silastic stent sutured to the forceps, and the stent pulled through the liver into the porta.

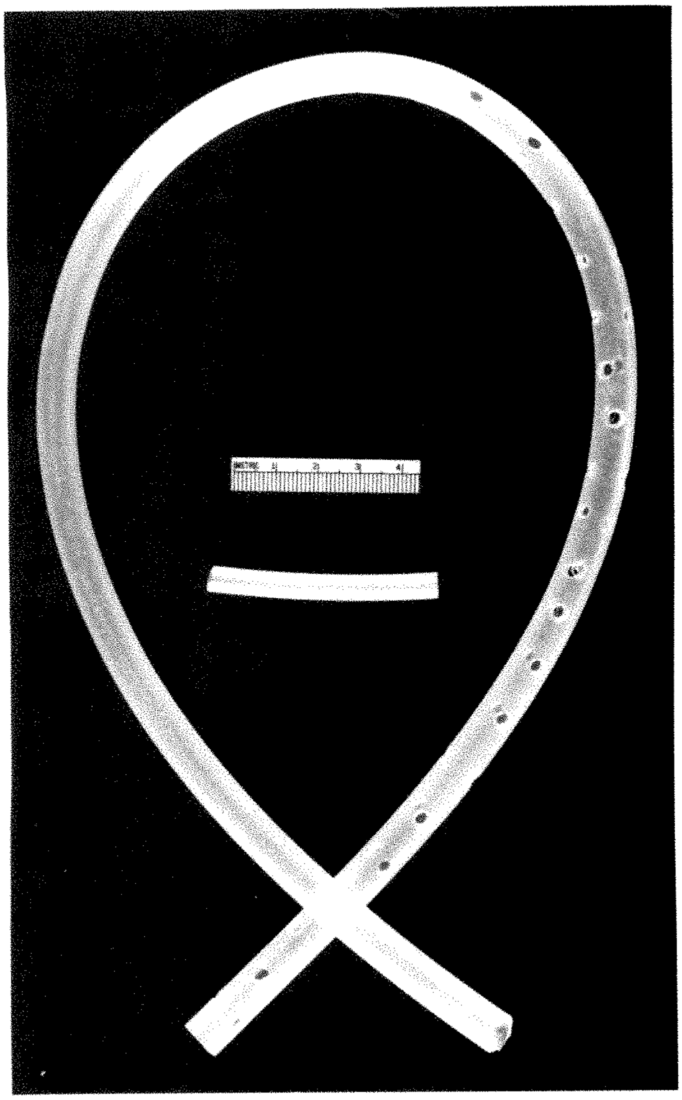


FIG. 4. The silastic stent is 60 cm in length and 1 cm in diameter. Multiple holes are placed in the distal portion of the tube. If the ductal system will not accept the large tube, a smaller 6 mm stent is used.

quired operative drainage. A third patient remained febrile for 10 days following surgery, but his temperature returned to normal with antibiotics. There were no operative deaths among these 10 patients, and no late deaths have occurred.

Followup in these 10 patients has ranged from one year and 3 months to 6 years and 6 months, and averages 3 years and 5 months (Table 2). No patient has required reoperation. There have been no instances of cholangitis. The serum bilirubin is normal in 9 of the 10 patients. The patient with strictures of both right and left hepatic ducts with two transhepatic silastic stents still in place, has a serum bilirubin of 4.0 mg/100 ml. The serum alkaline phosphatase remains elevated in 5 patients, and is normal or near normal in the remaining 5. The serum transaminases are mildly elevated in two patients, and in the normal range in the remaining 8 patients. All have resumed normal lives and are not limited in any way. One patient still has two transhepatic silastic stents in place and irrigates both tubes daily. Her activities are otherwise normal. Her silastic stents have been replaced as an outpatient on two occasions.

Discussion

Prior to performing the surgical repair of a benign stricture of the biliary tree, two options have to be dealt with. First, to what should the proximal biliary segment be anastomosed, and second, should the anastomosis be stented for a long period. In the past there have been strong advocates for anastomosing the proximal biliary segment to the distal common duct.[1] This often requires a tedious search for the distal segment since it is usually small and can be difficult to localize. In addition, once found there always is a wide disparity between the diameters of the two segments. Finally, the anastomosis will on occasion be performed under tension since a considerable length of duct usually has to be sacrificed to obtain normal tissue for repair. Others have advocated anastomosing the proximal biliary segment to the duodenum.[2,8] This eliminates the search for the distal biliary segment and any possible disparity in size when perform-

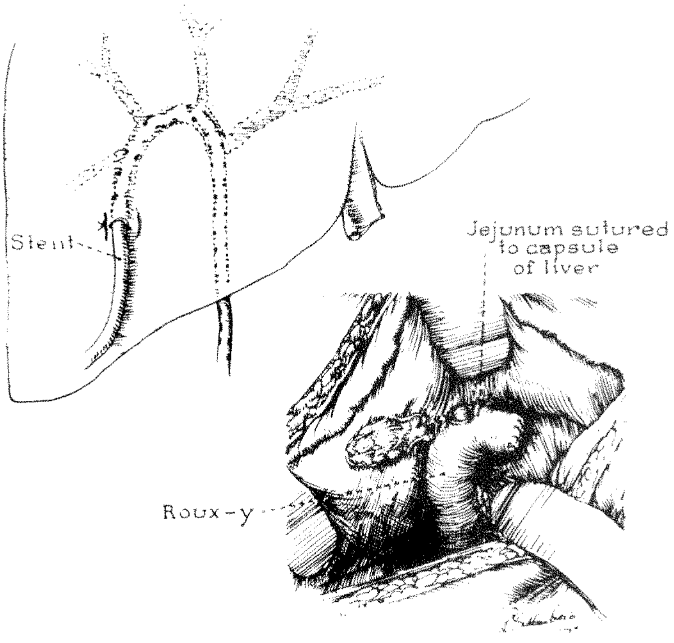


FIG. 5. A horizontal mattres suture is placed around the exit site of the silastic stent on the surface of the liver. The jejunal loop is tacked up to Glisson's capsule, or whatever tissue is available, and the silastic stent is placed into the jejunal loop through a stab wound.

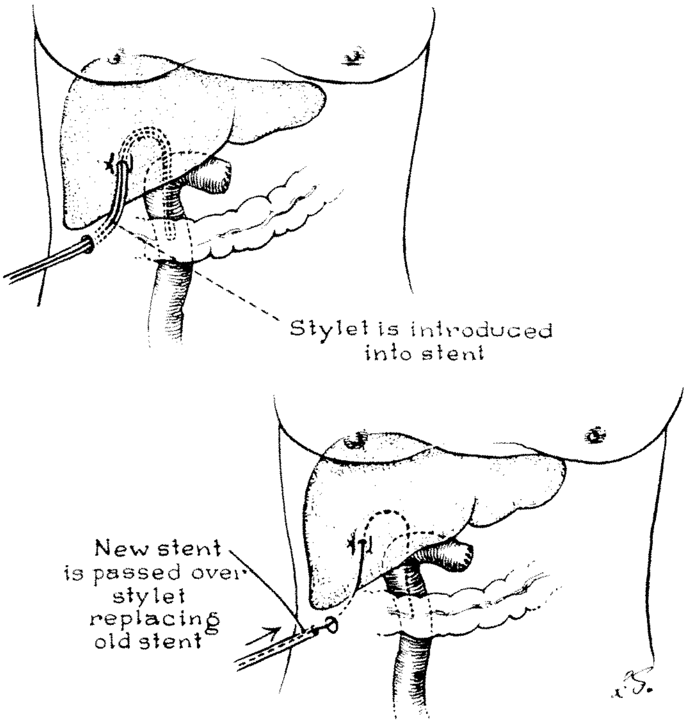

Stylet is introduced into stent
New stent is passed over stylet replacing old stent

FIG. 6. If the silastic stent becomes partially occluded with biliary sludge, it can be changed by first passing a flexible guide wire through the stent into the jejunal loop under fluoroscopic control. The old stent is removed leaving the guide wire in place. A new stent is then easily inserted over the guide wire.

ing the anastomosis. However, when dealing with a high hilar stricture, using the duodenum can make the anastomosis technically difficult and even result in tension on the suture line. Also, if the anastomosis leaks following repair, as it often does, in addition to a biliary fistula a duodenal fistula results. Using a defunctionalized Roux-en-Y jejunal loop eliminates the disadvantages of both the proximal biliary segment to distal common duct anastomosis, and the proximal biliary segment to duodenum anastomosis. The loop can be easily placed without tension in the hilum of the liver, and an end of biliary segment to side of jejunal loop anastomosis carried out without fear of tension or disparity of size. If a biliary leak occurs following repair, the enteric component of the fistula is of no consequence. Also, if the patient ever requires reoperation the area of the anastomosis can be more easily and safely approached. In using a Roux-en-Y loop the bile is diverted down stream in the small bowel and the risk of a duodenal ulcer is theoretically somewhat increased. However, the risk of a significantly shortened life expectancy is so high if a satisfactory biliary repair is not obtained, that the possibility of increased risk of peptic ulcer disease is secondary.

Whether or not to stent an anastomosis after repair of a benign biliary stricture remains controversial. There are proponents for long term stenting,[3,9,10] and those who feel a stent should be used only for a short period or not at all.[5,12] In performing a biliary tree to bowel anastomosis with good mucosal to mucosal approximation, as one does for instance after a pancreaticoduodenectomy for tumor, long term stenting is certainly not indicated or necessary. One might choose to insert a stent for short term decompression in case the anastomosis leaks initially, but many surgeons feel even short term stenting is not necessary. In repairing high hilar hepatic duct strictures, however, a completely different situation exists. In none of the 10 patients presented in this series was a proximal biliary segment available that contained reasonably normal mucosa around its entire circumference. In most instances the Roux-en-Y jejunal loop had to be tacked up to Glisson's capsule in the area that the silastic stent exited from duct and hepatic parenchyma, and good mucosal to mucosal approximation was not possible. Under these circumstances, long term stenting is mandatory. In the present series of patients the operative procedure created an internal biliary fistula between the biliary tree and a jejunal loop. Only after the scar tissue, which inevitably forms under such circumstances, has matured and contracted can one safely remove the stent. Using a large bore stent of silastic, which is known for its low tissue reactivity, may allow wound maturation to take place more rapidly and with less inflammatory response, and thereby de-

TABLE 2. *Most Recent Liver Chemistries in Ten Patients Following Stricture Repair*

Patient	Interval Since Repair (months)	Bilirubin (mg%)	Alk. Phos. (Int. U.)	SGOT (Int. U.)	SGPT (Int. U.)
E.N. #41 66 10	42	0.3	595	50	40
R.G. #148 65 12	37	0.2	34	13	9
L.T. #152 19 43	17	0.7	109	24	13
S.D. #155 99 49	15	4.0*	339	47	24
J.B. #137 70 54	47	0.2	42	20	20
A.V. #147 37 55	39	0.5	34	14	17
T.W. #131 40 59	78	0.8	110	22	
B.T. #146 37 65	39	0.2	51	29	24
J.L. #144 53 90	47	0.2	19	9	9
G.S. #143 20 94	51	0.8	29	11	7

* Two transhepatic stents remain in place.

crease the chance of late contracture. Surgeons from the Lahey Clinic have probably had more experience with biliary strictures than any clinic in the world. Their data clearly indicate that the longer one leaves a stent in place following repair, the more likely the repair will be successful.[10] A sizeable experience with stricture repair has also been gained at the Mayo Clinic, and they also advise long term stenting.[6]

The method of transhepatic stenting used in this series was first reported by Smith.[7] It allows one to firmly fix the stent so that migration is not possible, something we have seen with conventional T tubes. In addition, with the aid of a guide wire these stents can easily and quickly be changed as an outpatient procedure. Others have brought the distal limb of the stent out the jejunal loop and abdominal wall, creating a U tube to facilitate changing the tube. This clearly is not necessary as tube changes can easily and safely be made as above. Smith recommended rubber tubes be used, but we have found silastic to be superior. The silastic stents are very nonreactive, and biliary sludge accumulates on them much more slowly than on rubber tubes. On occasion we have seen silastic stents remain in place for up to a year without accumulating significant debris. Initial concern with the possibility of bleeding from liver parenchyma when the stent is brought out through the anterior superior surface of the right lobe has been unfounded, and we have had no instances of significant bleeding. Cholangiography postoperatively is easily performed by placing the patient in the steep Trendelenberg position (Fig. 7). This technique of stenting with transhepatic silastic tubes has also been used in our hospital with success for malignant biliary strictures.

All 10 patients presented in this series have done well. With an average followup of well over 3 years, there has not been a failure. No instances of cholangitis have occurred. Even though no length of symptom free followup guarantees that a patient will not restricture, the majority who are asymptomatic for 2 years following repair will never again have difficulties.[11] Close followup of all 10 patients continues in our hospital. Nine of the 10 patients have had their silastic stents removed. The bilirubin is normal in all 9. Only the patient with strictures of both right and left hepatic ducts, and with two silastic stents still in place, remains chemically jaundiced. She is now 15 months post surgery and we plan to leave the stents in place permanently because of the technical problems associated with repair. This patient has all of the left hepatic duct drained, and part of the right hepatic duct. Since patients ordinarily require only 50% of their liver parenchyma to completely clear serum bilirubin,[4] theoretically she should not be jaundiced. It is possible, however, that she incurred enough liver injury during the prior two attempts at repair that she no longer is able to clear bilirubin with the amount of liver being drained. Nevertheless, she is totally asymptomatic and living a normal unlimited life. The success obtained in these 10 patients with this technique of long term transhepatic stenting with a large bore silastic tube and the ease with which the repair can be carried out after the proximal biliary segment is identified, leads us to recommend this approach for all high hilar hepatic duct strictures.

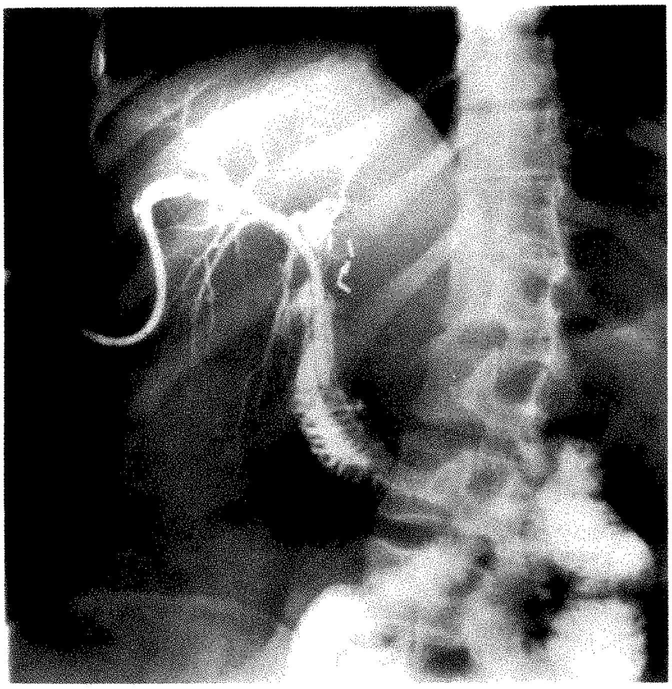


FIG. 7. A postoperative cholangiogram obtained by injecting the transhepatic silastic stent in a patient (L.T.) who previously had undergone repair of a high hilar hepatic duct stricture. Note that with the multiple side holes in the stent, there are no signs of obstruction of hepatic duct branches by the stent.

Addendum

Patient T.W. recently returned with a serum bilirubin of 3 mg %, 6 years and 9 months after his repair. A transhepatic cholangiogram revealed a stricture of his left hepatic duct. A transhepatic stent was easily reinserted through his Roux-en-Y loop. His bilirubin is now normal and it is planned to leave the stent in place for 12 months.

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DISCUSSION

DR. KENNETH W. WARREN (Boston): I think this is a very excellent presentation of one method of repairing high hilar strictures of the common duct and the hepatic duct. As a matter of fact, most of the strictures that we see are high. Usually we can identify the lining of the duct, even if the duct should then divide above the bifurcation. But one must bear in mind that individualization, both in the choice of an operation and in the choice of a stent, is really the hallmark of repair of common duct strictures.

We agree that the use of a transhepatic straight tube has several advantages, as pointed out by Dr. Zuidema. First of all, you can get x-rays, if you wish. They are usually not necessary if the patient is having no symptoms. You can irrigate the tube, and, most importantly, as I think Dr. Zuidema would agree, this tube can be changed. Now, we've used several of these, and we use it almost routinely in inoperable carcinoma of the bile ducts at the hilus, and frequently, as shown in one of his cases, we use bilateral transhepatic intubation.

For my own part, the high strictures in the hilus of the liver are usually repaired by using a modified Y-tube stent with the mucosal bridge, and even if you cannot identify—which we usually can—the lining of the duct, by placing this properly and by making the bridge sufficiently wide, one can insinuate the mucosa up into these two ducts.

Or if you are going to use the method with the straight transhepatic tube, as most of you know, Rodney Smith recently has used a different type of mucosal graft, pulling it up into the liver, into one duct or the other, and I'm sure that this has a great deal of merit.

So I think this is a wonderful experience that has been reported here today, and as Dr. Sandblom mentioned, you're going to have to follow these patients for many years, because we have seen strictures occur ten, 15, 20 years after an excellent repair and a long-term result.

As far as the modified Y-tube remaining in place without symptoms, practically all of them will remain in place without evidence of cholangitis for a year; so that this is a method that Dr. Zuidema has reported, it has merit, and I shall follow with great interest the long-term results.

DR. H. WILLIAM SCOTT, JR. (Nashville): Dr. Zuidema knows very well that Dr. William Halsted was greatly opposed to the use of stents, or any form of inlying tube, in biliary anastomoses, but I don't believe Dr. Halsted dealt with the terrible fibrotic strictures that are currently under discussion. As Dr. Warren has pointed out, a great deal of the experience with the repair of biliary strictures that we have had in this country has derived from the experience of his former chiefs, the late Frank Lahey and Richard Cattell, at the Lahey Clinic. We have also learned much from the late Arthur Allen at the Mass. General, Dr. Waltman Walters at the Mayo Clinic, and Warren Cole, who is currently here in this audience.

(Slide) Dr. John Sawyers a few years ago presented to this Association the experience that our group in Nashville had at that time with the use of Dr. James Kirtley's fishmouth method of handling the scarred, fibrotic proximal hepatic duct with Roux Y jejunostomy. Only three patients had a stent. This shows the artist's illustration of the surgeon's dilemma as it seemed to us at the time, whether to use a stent or not. And our meager evidence certainly supports the contention that Dr. Zuidema's more powerful evidence brings about.

There were five recurrent strictures in nineteen patients without a stent, and in three patients who had a stent no strictures occurred.

I'd just like to ask if Dr. Zuidema would tell us whether Dr. Rodney Smith's extensive experience with the use of transhepatic stenting has been accompanied by much in the way of complications. One worries, of course, about traumatic hemobilia, which we heard Dr. Sandblom talk about this morning, and one also wonders about the incidence of stress ulcer with biliary diversion. I didn't notice any stress ulcers in the complications listed by Dr. Zuidema. I wondered if he used any particular method of preventing stress ulcers, such as routine use of antacids in the postoperative period.

And, finally, I wish he would say a bit more about the management of patients, antibiotics, irrigations, how to prevent the complications of infection with an in-lying tube.

DR. FRANK C. SPENCER (New York City): Dr. Rodney Smith has been referred to several times, and I thought it would be of interest to the organization to describe some of our visits at St. George's with Sir Rodney last September.

I was quite overwhelmed by the extent of his experience, his absence of complications, and his impressive movie. He cites experiences with about a thousand patients with common duct strictures over the past 20 years and the uses of his mucosal tube technique. He is free to admit that he does not have good long-term followup, but the short-term followup, in terms of morbidity, mortality, and the like, is extremely small. I came away with the very simple question of "Why in the world, as we both speak English, aren't we using it more?"

So I rise with hearty support of Dr. Zuidema's position. And, if you will note, in his presentation, quite strikingly, all ten of their cases developed temporary leaks that healed in the majority.

A striking feature of Sir Rodney's technique is that he forms his mucosal tube, places the stent as described, anchors it to the tube with one stitch, and pulls it up over the stricture, with no stitches whatever, except one or two to anchor it to the hilum of the liver, treating it like an onlay graft.

I think that's probably the difference from the technique that Dr. Kirtley was so innovative with in Nashville, in that he sewed it around the hilum of the liver, but could not get mucosal-to-mucosal apposition, hoping that the scar tissue would bridge. But by tying the mucosal tube to the stent and tugging it upward, it's actually implanted like a skin graft.

As many have said, you must have long-term courses. I think there is no question from the abundance of data that we have been far behind in this technique, or adopting it for awkward problems, to lessen morbidity, and, ideally, for the patient with malignant stricture, who is certainly the candidate for permanent intubation with this technique for as long as they live. I hope papers like Dr. Zuidema's will do much to popularize it in this country. Thank you very much.

DR. JONATHAN E. RHOADS (Philadelphia): We attempted a slightly different approach several years ago with a patient who had had five unsuccessful attempts to correct stricture. After sealing off the pleural sulcus, we went up the common duct with a urethral sound, at the suggestion of Dr. Oscar Batson, and pushed through to the chest wall with this, and drew a heavy nylon cord, such as used on parachutes, through. We had a defunctionalized loop already in place, anastomosed to the lower end of the bile duct, end of bile duct to side of loop, and the end of the loop coming up here in the epigastrium. So this cord went back in the jejunal loop here, up through the stricture, through the ducts, and out through the side. We were able to tie bougies on it and dilate this at will, and finally taught the patient to pull the bougies around himself.

We thought we had him cured. He went, I think, about six years, but toward the end of this time he began to show signs of hepatic deterioration, as so often happens with these people, and eventually succumbed.

To speak of another long-term failure, we had a woman who, after a number of operations and, I think, six or eight years' stenting with a series of T-tubes, had a T-tube wear out, and we simply removed it. She had no trouble for, I think three and a half years, and again we thought she was cured, but her stricture recurred in the fourth year.

So I am interested that some of these patients have already gone well over five years. I think that a few years is worthwhile. It may be premature to predict what the long-term results are, not only from the standpoint of stricture, but from the standpoint of the way the liver parenchyma stands up. Nevertheless, I feel this is a real advance, and certainly congratulate the authors.

Dr. John L. Cameron (Closing discussion): In response to Dr. Warren, certainly the Lahey Clinic has more experience with benign hilar strictures than any clinic in the world, and their results certainly are those to which all of us must compare ours. We have used the Y-tube, not nearly as extensively as at the Lahey Clinic, but find that in our hands the main disadvantage is that it becomes occluded and cannot easily be changed. Silastic cannot be used for a Y-tube or a T-tube that has a long track through the peritoneal cavity, because when the Silastic tube is removed, no matter how long the interval, the track is not secure enough to prevent bile from leaking into the peritoneal cavity. Therefore, a transhepatic stent really has to be used if one is to use Silastic.

In response to Dr. Scott, we certainly agree with his results published previously that a long-term stent seems preferable to using a short-term stent or no stent at all. It's interesting that he mentioned Dr. Halsted's aversion to stenting or to T-tubes. According to Dr. Willian Rienhoff, Jr. this arose from the fact that after Dr. Halsted's first common duct exploration, performed on Dr. Halsted, when his straight bile duct catheter was removed, he developed a biliary cutaneous fistula that remained open for many weeks, and sent Dr. Rienhoff to the Hunterian Laboratory to try and work out techniques of primary suture of the common duct.

Following the initial two-week period after the stent has been placed, and the biliary fistula is closed, we do not use long-term antibiotics, and have had no episodes of cholangitis while the stent remained in place. The patient does irrigate the tube once or twice a day at home, unclamping it to irrigate with sterile saline, and we have kept many of these patients on various choleretic agents, such as Zanchol, to maintain a very high biliary flow, but have not had trouble with cholangitis while the stent was in place. But we do change them frequently, if they become partially occluded with sludge.

I certainly agree with Dr. Spencer that Sir Rodney Smith is a very innovative and imaginative biliary and pancreatic surgeon. I think we owe many of the contributions over the last ten and twnety years in this area to him. I think our technique is really very similar to his, and, of course, ours is copied and derived and modified from his technique. It's interesting that he also has a high incidence of biliary cutaneous fistulas temporarily postoperatively.

I'd like to thank Dr. Rhoads for his comments. Fortunately, we have been able to dissect the hilum and find the proximal segment in all of our patients, but I think if one cannot do that, either the Longmire procedure, or his technique, might be applicable.

The Fate of Esophageal Varices Following Selective Distal Splenorenal Shunt

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JOE U. LEVI, M.D., EUGENE R. SCHIFF, M.D., PAT FINK, R.N.

Esophagographic evaluation of the fate of esophageal varices after distal splenorenal shunt was obtained. The radiologist-observer was blinded as to the surgical status of the films under study. The results indicate that varices are likely to persist after surgery. However, the sizes of the varices are clearly diminished following selective distal splenorenal shunt. The incidence of postoperative bleeding has been low, 3.7% (2/54) or one episode for each 441 months of postoperative survival.

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THE PERSISTENCE of esophageal varices following portal-systemic decompression is well documented. Palmer has reported the incidence of such persistence to be 27% after portacaval shunt and 83% after conventional splenorenal shunt.[6] These observations were made endoscopically, the technique considered to be the most precise method for evaluation of esophageal varices. The disadvantages of esophagoscopy for long term assessments in our experience are: 1) it is an invasive test and, 2) patient acceptance under the doctorine of informed consent is low. For these reasons, this retrospective, non-randomized but blinded study presents the results of radiological assessment of the fate of esophageal varices after the construction of selective distal splenorenal shunts.

Methods

X-ray films of barium studies of the esophagus of 26 patients who were followed from one to 4 years after surgery were considered adequate for this study. All of the radiographic examinations were conducted at a time when the patients were not bleeding. Code numbers were assigned to the films and all other identifying characteristics were obliterated. The major problem in this endeavor was to mask the metallic clips seen on most of the postoperative films. This was solved by painting over each clip on the postoperative films and in similar locations on the preoperative films (Fig. 1). This served to conceal the surgical status of the patient whose films were being assessed. Subsequently, all of the films were read by one radiologist and the varices were graded on a 0–4+ scale. Representative examples of x-ray films reflecting the evaluations are seen in Figs. 2 and 3.

Results

Analysis of the grades awarded to the x-rays by the radiologist revealed 5 patients (19%) in whom the varices were unchanged for the entire period ranging from 1–4 years after surgery (Table 1). In one of the 5 patients the varices were thought to be one grade larger in the second postoperative year, although this patient has not bled during this interval. In 4 patients (15%) complete disappearance of the varices was recorded and in the remainder of the group, 17 (65%) the varices were noted to be smaller in size but definitely identifiable as persistent (Fig. 4).

At one year after distal splenorenal shunt the x-ray films of 18 patients in the group of 26 were available for

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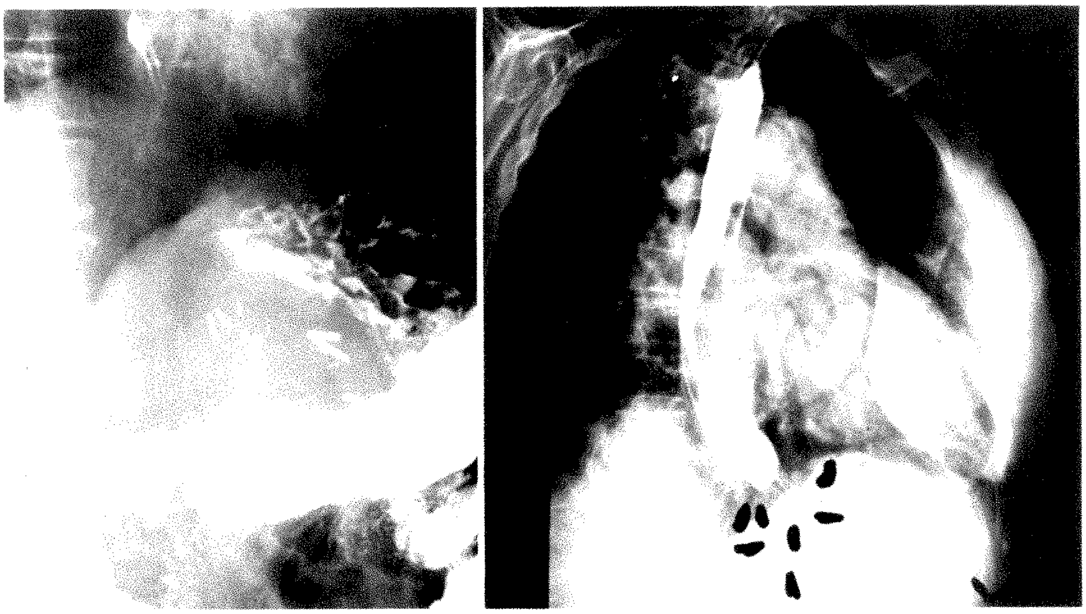
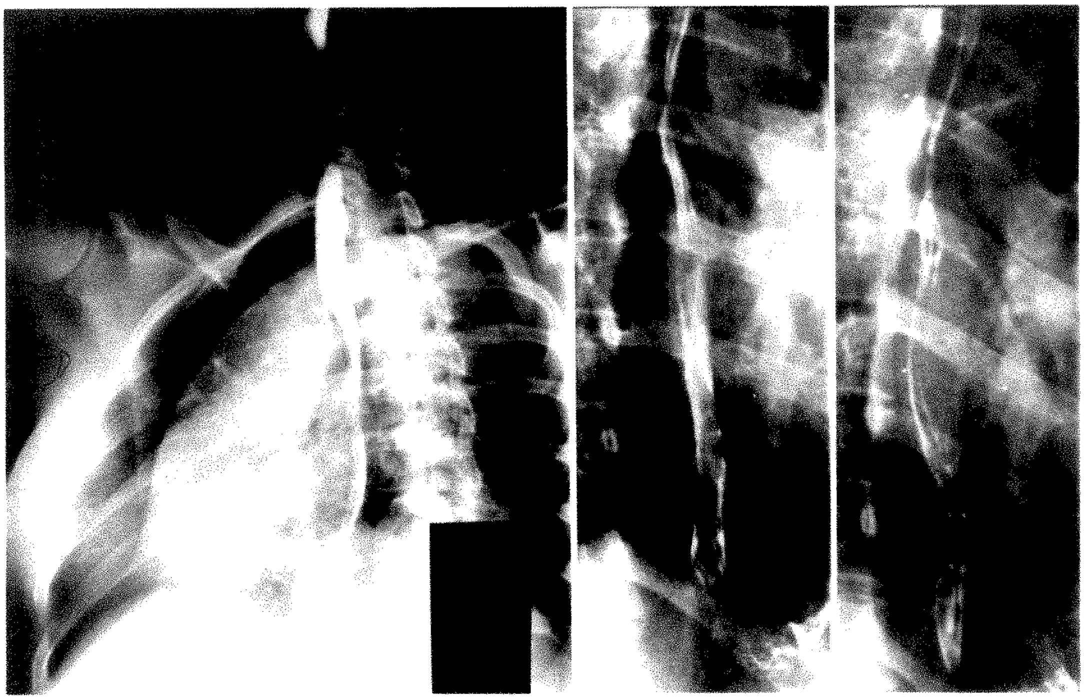


FIGS. 1a and b. (left) Typical postoperative radiograph showing multiple clips. (right) Clips marked out with black paint. All of the films of each patient were painted in locations similar to the postoperative studies.

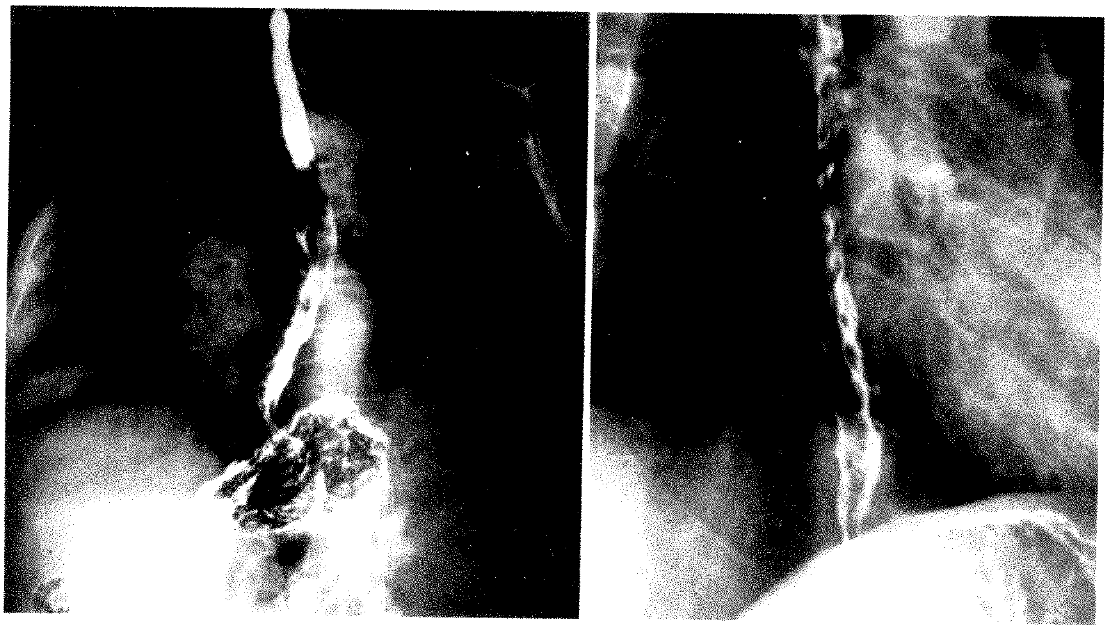
study. Another two patients were noted to show no decrease in variceal size during the one year interval. However, even at this time, a difference is noted in the distribution of the numbers of patients in each grade cell (Table 2). Eighteen of the 26 preoperative patients were graded 3+ or 4+ whereas 9 of the 18 patients evaluated at one year after surgery were considered to have none or 1+ varices. The percentage occupancy of each grade cell is demonstrated in Fig. 5 wherein an obvious distinction between the preoperative and postoperative groups may be seen. More than 70% of the postoperative patients are found in the cells 0 to 2+ whereas almost 90% of the preoperative patients occupy the cells identified as grades 2+ to 4+.

Discussion

The accuracy of esophagography for the diagnosis of esophageal varices continues to be questioned.[1,2] As a



FIGS. 2a and b. (left) Grade 1+ varices. (right) Two views of 2+ varices.



FIGS. 3a and b. (left) Grade 3+ varices. (right) Grade 4+ varices which extend to the thoracic inlet.

rule, it seems that esophagoscopy will demonstrate varices in 90% of the instances while conventional esophagography may result in the correct diagnosis in 70% of similar cases.[5,8] However, the accuracy of endoscopy per se is not perfect since observer variability may approach 30%.[3] In this study, comparative accuracy was not considered and the relative merits of different techniques of evaluation were not studied since it seemed more important to blind the observer as to the fact of the patient's therapy. In addition, patient acceptance of the evaluation was deemed more important in order to obtain sufficient data for analysis.

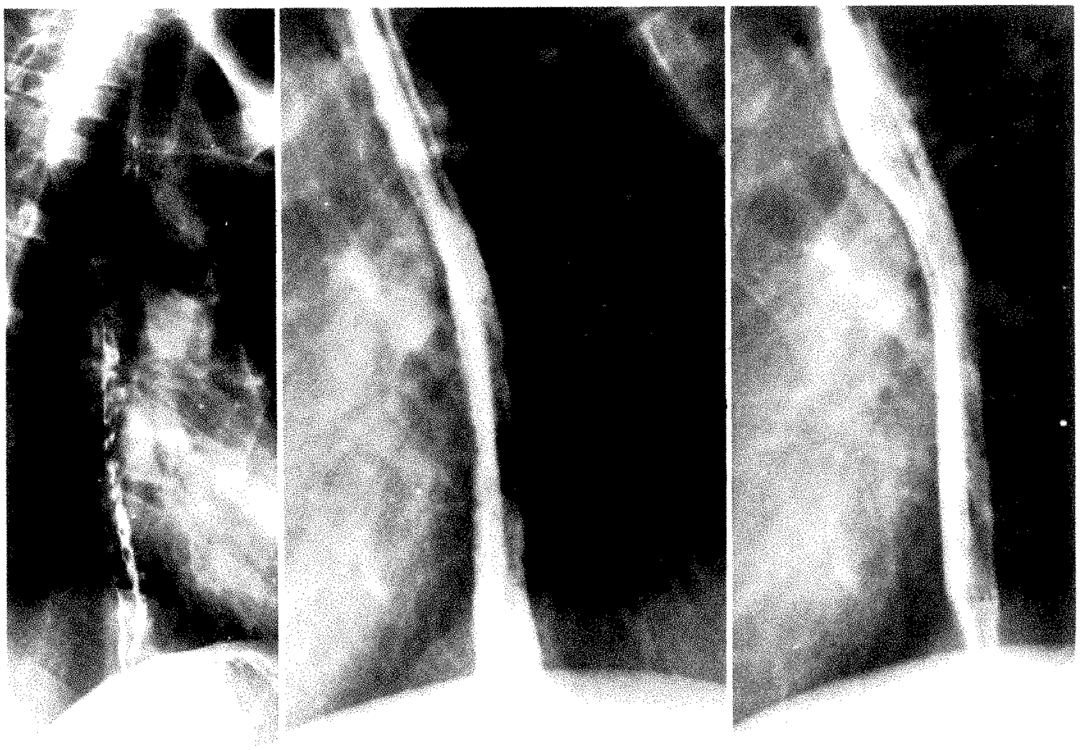
TABLE 1. *Time After Distal Shunt*

Pt. #	Preop	1 yr	2 yrs	3 yrs	4 yrs
1	4+	4+*	2+	—	1+
2	2+	—	—	1+	1+
3	4+	3+	—	—	—
4	2+	0	0	—	—
5	4+	—	1+	—	—
6†	2+	2+	3+	—	—
7	4+	—	1+	—	—
8	4+	0	—	—	—
9	2+	1+	—	—	—
10	4+	1+	—	—	—
11	3+	1+	—	—	—
12*	1+	1+	—	—	—
13*	2+	2+	—	—	—
14	3+	2+	—	—	—
15	4+	3+	—	—	—
16*	3+	3+	—	—	—
17	4+	1+	—	—	—
18*	3+	—	—	—	3+
19	3+	2+	—	—	1+
20	4+	—	—	2+	3+
21	4+	4+*	1+	1+	—
22	4+	—	2+	—	—
23	3+	—	0	—	—
24	3+	—	1+	—	1+
25	1+	0	—	—	—
26	2+	1+	—	—	—

Varices graded: 0 (none), 1+, 2+, 3+, 4+
— No observation.
* Varices unchanged.
† Varices worse.

The data presented suggest that the distal splenorenal shunt has a beneficial effect on the size of esophageal varices as has been demonstrated for other shunt operations. However, in 85% of patients some degree of persistence of varices was noted. This finding is also similar to those reported after conventional shunt therapy, although the techniques of evaluation have differed. For the most part, the other studies have used esophagoscopy for which the observers were not blinded as to the patients' therapies. In this manner, Dagradi has concluded that varices do not disappear after portacaval shunt "except in rare instances." His esophagoscopic evaluation did reveal a reduction in the caliber and extent of varices after shunt therapy, a finding similar to that seen on esophagography in this study.[4]

Perhaps the most important point at issue is the significance of persistent varices with regard to the risk of subsequent variceal hemorrhage. Palmer has considered that spontaneous fluctuation in variceal size is of sufficient magnitude to preclude the usefulness of the persistence of varices as the criterion for judging the success of portal decompression. He has written that: "prevention of variceal bleeding remains the best test of shunt effectiveness."[7] In our series of 54 consecutive patients followed from one to 51 months after elective distal splenorenal shunt, only two bleeding episodes have occurred. This



FIGS. 4a and b. (left) "Wall to wall" varices extending above aortic arch. (right) Striking reduction on postoperative films.

TABLE 2. *Comparative Analysis of Grade Evaluations*

Preoperative		1 Yr Postop	
Grade	No. Pts.	Grade	No. Pts.
0	0	0	3
1+	2	1+	6
2+	6	2+	4
3+	7	3+	3
4+	11	4+	2
Total	26	Total	18

18/26 patients were in grades 3+ and 4+ preoperatively, compared to 13/18 patients in grades 0 to 2+.

represents two occurrences in 883 patient-months of study. Precise identification of bleeding from varices was not obtained in either patient, however, it has been attributed to variceal origin since no other site for bleeding could be demonstrated.

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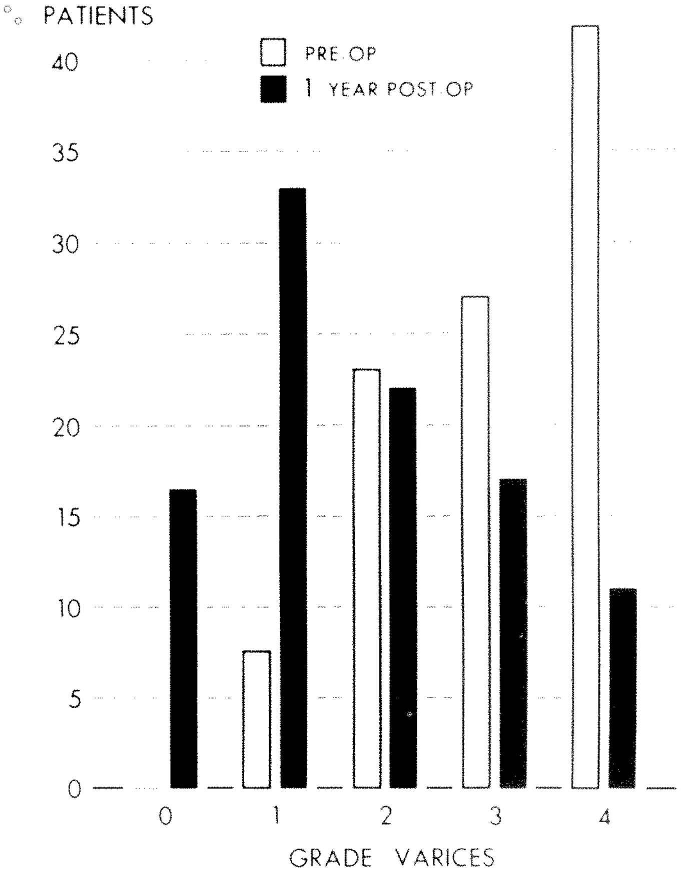

FIG. 5. Change in percentage distribution of patients in grade cells 0 to 4+ postoperatively as compared to preoperative assessment.

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DISCUSSION

DR. SESHADRI RAJU (Jackson, Mississippi): In Jackson we thus far share the enthusiasm of Dr. Zeppa for this distal splenorenal shunt, and we hope that its apparent superiority over the other shunt procedures will become firmly established. Nevertheless, it has some drawbacks. It is technically a somewhat difficult operation, often time consuming, and may require fair amounts of blood. It is certainly not the procedure for the surgeon who does only an occasional shunt, moreover, for the same reasons, it is not an ideal emergency procedure.

(Slide) The anatomical feature which makes this operation tedious is the multiple pancreatic branches of the splenic vein. Thus, we looked for, and have devised, a modification which we think will minimize or obviate several of these objections I stated.

In a recent patient, we excised a portion of the autogenous jugular vein, and simply used it as a jump graft between the splenic vein and the renal vein. The splenic vein was tied proximal to the jump graft. In effect, therefore, this is a Warren shunt, except that the modification provides certain distinct advantages.

Firstly, one has to clear only 4-cm segment of splenic vein, and we don't have to mobilize the whole length of the splenic vein, as in the original Warren procedure. This makes the technical exercise much easier. Furthermore, you have to clear only the superifical aspects of the splenic vein, leaving the deep pancreatic branches intact in the 4 cm segment. You clear the splenic vein just enough to place a partial occlusion clamp to sew the jump graft in.

As I said, this maneuver significantly reduces the operating time and blood loss.

(Slide) You can see the jump graft here: (indicating) the splenic vein has been tied off. This is the renal vein and these are the numerous pancreatic branches of the splenic vein.

(Slide) This shows the jump graft in position. You can see that the internal jugular vein is fairly large: in fact, slightly larger than the splenic vein.

(Slide) The jump graft effectively reduces distal splenic pressure, while maintaining the portal pressure intact, the primary principle of this operation.

(Slide) The next slide shows the postoperative contrast study. This is an arterial injection, venous phase. You can see the jump graft and the renal vein; you can even see part of the vena cava, opacified due to the nicely functioning shunt.

DR. GEORGE JOHNSON, JR. (Chapel Hill): The treatment of these unfortunate patients with bleeding esophageal varices is in a state of flux at the present time. The long-term results of the portacaval shunt as they are presently being reported are not very promising. Although the long-term results of the ablative operation, championed by Dr. Nathan Womack, are promising, the immediate mortality and recurrent episodes of bleeding are certainly distressing.

Of the twenty-six patients that we have had the opportunity of examining the status of their esophageal varices following an ablative operation, 27%, compared to the 8% just reported, have had complete disappearance of their varices. On the other hand, in 46% there was no change, and in only 19% did the size of the varices decrease. In 7% the varices actually increased in size following the ablative procedure.

It is our present feeling that the ablative operation should be restricted as a primary operation to good-risk patients with severe hypersplenism.

Currently, the primary operation used at our institution is the interposition mesocaval shunt, popularized and championed by the late Dr. Ted Drapanas. It is certainly appealing in its relative technical simplicity. Although we have performed several distal splenorenal shunts as described by Zeppa and Warren, and are satisfied with the results, we find it to be a tedious procedure that should be performed by a select group of surgeons.

If, however, the operation will allow liver perfusion, and yet decompress the varices, is associated with a low morbidity and mortality, and episodes of recurrent bleeding, then most of us who are operating upon these patients would be willing to spend the time and effort necessary to perform this procedure. The data just presented support increasing utilization. We shall, therefore, look forward to hearing increasing reports of long-term evaluation of the selective distal splenorenal shunt, not only from Zeppa and Warren, but also from other centers utilizing this procedure.

I would like to ask Dr. Zeppa if the increase in the size of the varices can be correlated with portal pressure, or other hemodynamic or clinical data.

This study is important, because the distal splenorenal shunt has apparently decompressed the varices, as Zeppa predicted, without significantly lowering portal vein pressure. I must admit that I have been a skeptic.

DR. ROBERT B. SMITH, III (Decatur, Georgia): We wish to emphasize that the selective distal splenorenal shunt under discussion is a multiple step operative procedure that involved not only decompression of the distal stump of the splenic vein, but also, very importantly, portal-azygous disconnection by ligation of the coronary vein and the right gastroepiploic vein. Without these important steps, this operation amounts to little more than a remote total shunt. Nabseth recently reported an experience in which he deliberately failed to ligate the associated veins, and observed a significant incidence of rebleeding and encephalopathy among his patients. Others have had similar results when inadvertently the ligations were not performed.

In our experience with more than 50 distal splenorenal shunts over the last four years at Emory, no patient has died of rebleeding if the shunt remained patent. We also have noted persistence of the varices on endoscopy and G.I. Series following operation, just as is the case with total shunts. We assume that the protective effect of the distal shunt relates to reduced pressure in the regional veins, and even though the varicosities may persist anatomically, these patients have no greater incidence of bleeding than with total shunts.

DR. WILLIAM SCOTT, JR. (Nashville): Some of us had an opportunity to hear Dr. Sandblom's colleague, formerly at Lund, now at Boras, Sweden, Dr. Carl-Axel Ekman, comment on his use of the Warren shunt in some 40 patients. He continued to study these patients, and found that a large number of them apparently had encephalopathy, and he has stopped doing the procedure, and has reverted to—or continued to use—the end-to-side portacaval shunt.

I don't know any more about this than what I heard in Sweden, but do want to have comments from Dr. Zeppa, and perhaps Dr. Warren.

DR. W. DEAN WARREN (Atlanta): From my conversations with Dr. Bengmark, it is my understanding that they have utilized the procedure in those patients primarily with chronic active hepatitis. If one takes this tack, there are going to be many patients who go ahead and die of progressive hepatitis and ultimately hepatic failure. If one calls that encephalopathy, which is what Dr. Bengmark was speaking about, then there will be many instances of hepatic encephalopathy.

I will once again call your attention to the fact that there is a prospective controlled randomized study comparing the selective splenorenal shunt with the total shunt, which in this study are primarily mesocaval and mesorenal H-grafts. As of the last time this was reviewed, which was recently, there were nine proven cases of encephalopathy in the total shunt group where there was only one in the distal splenorenal shunt group. This is a highly significant difference. As far as survival is concerned, the selective splenorenal shunt is also currently superior to the total shunt, but this is not significant at the present time.

Let me once again emphasize that the Lund experience has been gained primarily in the treatment of chronic active hepatitis in cirrhosis, and one certainly cannot relate this to the stable cirrhotic, which is a group we feel should be shunted and is the group we are studying at Emory.

Dr. Duane G. Hutson, Sr. (Closing discussion): I want to make just a few comments. Use of an autogenous vein as an H graft might have some technical advantage in selected cases; however, we don't feel that this is necessary as a routine.

We have emphasized the importance of preoperative angiographic evaluation and continue to recommend this very strongly. These studies will identify the patient with unsuspected thrombosis of the splenic and/or portal vein, as well as anatomic problems that might preclude the performance of a shunt.

If the distal shunt is to replace the portacaval shunt as the procedure of choice in variceal hemorrhage, it must accomplish the following: 1) prevent recurrent hemorrhage; 2) decrease the incidence of postoperative encephalopathy; 3) be associated with a low operative mortality; and 4) prolong life.

Our present series consists of 55 patients followed from one to five years. During this interval, there have been only two rebleeds. One was a minor bleed, which did not require transfusion. The other was severe occurring six months after an end renal to side splenic anastomosis. Patency of the shunt was not verified by arteriography. From this series and others it is unquestionable that the distal shunt is effective in the prevention of hemorrhage from gastroesophageal varices.

Over the past four years, we have performed 55 elective shunts on an unselected group of patients, without an operative death. Similar reports from other institutions are appearing with increasing frequency. The original criticism of an unacceptable operative mortality has been laid to rest.

These 55 patients have been evaluated extensively regarding the development of encephalopathy. At this point, only one patient has developed clinical encephalopathy. This rate is far below that expected following a portacaval or mesocaval shunt and probably represents what one might expect in a non-shunted group of cirrhotics. It is clear that the incidence of postoperative encephalopathy is greatly reduced following a distal shunt as compared to all other central shunts.

The only factor remaining to be proven is the effect on survival. At this point in our series, the five-year survival is significantly improved as compared to that reported following portacaval shunts. The numbers, however, are too small to draw any definitive conclusions at this time.

Retrospective Analysis of 100 Consecutive Patients Undergoing Related Living Donor Renal Transplantation

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One hundred consecutive patients receiving related donor kidneys were analyzed in regards to graft and patient survival, morbidity, mortality, histocompatibility and rehabilitation. The average followup was 3 years and 2 months with a minimum post transplant evaluation of one year. Donor morbidity was minimal and the mortality nil. Recipient mortality was 17%, all of which occurred after the first two post transplant months. The most serious life threatening complications after transplantation were due to infection. The greatest morbidity was secondary to aseptic necrosis. The overall graft survival at one year was 94%, 2 years—87%, 3 years—81% and 4 and 5 years—72%. Separation of patients according to tissue typing revealed 95% of recipients with A and B matched kidneys to be alive 5 years later compared to 55% of patients receiving C and D matched kidneys. Rehabilitation was good to excellent in 76% of the living patients and poor in only 4%. These results suggest related donor renal transplantation to be the treatment of choice for patients with chronic renal failure excluding only those individuals who are exceptionally high risks in terms of morbidity and mortality.

SUCCESSFUL TREATMENT of patients with end stage renal failure can be accomplished by either long-term hemodialysis or renal transplantation. It is accepted that patients with well functioning kidney transplants have a better state of health and overall rehabilitation than those on chronic dialysis. Recipients of HLA identical kidneys have an excellent prognosis for both graft and patient survival.[8,24] The results are less successful when the recipient is mismatched at one antigen and definitely worse when there are two antigen mismatches. Additional factors such as age, diabetes, history of myocardial infarction or gastroduodenal ulcer disease all predispose to an increased incidence of morbidity and mortality in renal allograft recipients.[17] Therefore, the risks of transplantation versus those of chronic hemodialysis must be carefully weighed when formulating a management program for the patient with chronic renal failure.

The following study reviews the first 100 consecutive renal transplant operations involving recipients of related living donor kidneys at the University of Alabama Medical Center. The information accumulated is pertinent in selecting patients for either long-term dialysis or transplantation.

Clinical Material and Methods

Recipient Patients. Ninety-eight patients received 100 renal allografts from living related donors between May, 1968 and July, 1975. Two patients received a second transplant after their first graft failed. Sixty per cent were between the ages of 21 and 40; 69% were male and 85% were Caucasian (Table 1). Forty-five per cent of the kidneys were donated by parents, 54% by siblings and one by a daughter (Table 2). The primary renal diseases causing renal failure included glomerulonephritis in 70%, pyelonephritis in 16%, polycystic disease in 7% and arteriolonephrosclerosis in 5%. One patient lost his kidney to renal trauma and another had congenital dysplasia (Table 3).

Tissue Typing. Histocompatibility matching, performed by a modification of the cytotoxicity technique of Amos, was completed prospectively in all donor and

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TABLE 1. *Age, Sex and Race of 100 Consecutive Recipients of Related Donor Allografts*

Age	No. Patients
0-10	3
11-20	15
21-30	42
31-40	18
41-50	21
51+	1
Sex:	Race:
Male 69	Negro 15
Female 31	Caucasian 85

TABLE 3. *Cause of Renal Failure*

Disease	No. Patients
Glomerulonephritis	70
Pyelonephritis	16
Polycystic Disease	7
Arteriolonephrosclerosis	5
Renal Trauma	1
Congenital Dysplasia	1

recipient patients. Patients were classified according to their response: A—identical, B—not identical but no antigen mismatches, C—1 antigen mismatch and D—2 or more antigen mismatches (Table 4). Genotypic analysis was performed in 98 patients. No transplant operations were performed in patients with two haplotype mismatches. A recipient serum-donor lymphocyte crossmatch was performed prior to transplantation.

Transplant Management. Seventy-three patients before transplantation required bilateral nephrectomy for hypertension, chronic urinary tract infection and on occasion for anti-glomerular basement membrane antibodies detected in the serum. All patients but one were prepared by hemodialysis. The transplant procedure was performed by the standard extraperitoneal approach in 97 patients using end-to-end renal artery-hypogastric artery anastomosis or end-to-side renal artery-external iliac artery anastomosis. All venous anastomoses were completed using the end-to-side renal vein-external iliac vein technique. In three children the graft was placed intra-abdominally using the aorta and vena cava for the vascular anastomoses.[23] A ureterovesical anastomosis was performed in every instance and perinephric drains were used only in the first 5 patients. The fluid management program has been described.[6]

Immunosuppressive Management. All renal allograft recipients received azathioprine and prednisone and 75 were treated in addition with antithymocyte globulin (ATG) prepared and administered as noted previously.[5] Acute rejection was defined as an increase in the BUN 10 mg/100 ml and in the serum creatinine 0.5 mg/100 ml above the previous stable level of renal function in the absence of urinary tract obstruction. Renal scans and estimated renal plasma flow were often helpful in separating rejection from nonimmunologic causes of impaired renal function. Additional factors assisting in the diagnosis of rejection were weight gain, fever, hypertension and an increase in renal size associated with tenderness to palpation. Acute rejection was treated by increasing prednisone to 5 mg/day with rapid reduction to near prerejection levels during the next 10 days. In some instances one gram of intravenous methylprednisolone was administered in 3 separate dosages every other day in conjunction with increasing the oral prednisone. Allograft irradiation, totalling 600 r to the mid-plane of the kidney was given in 4 divided doses of 150 r each. Forty-one patients were selected for conversion from daily to alternate day prednisone therapy. Twenty of these patients obtained kidneys from parents, 20 from siblings and one from an offspring. The indications for conversion included obesity—17 patients, aseptic necrosis—9 patients, enhancement of growth—8 patients, cosmetic—6 patients and cataract formation—1 patient. Sixteen of these 41 patients received A or B matched kidneys and 25 were C or D matches.

Postoperative Followup. All post transplant patient management was conducted in the transplant clinic. Blood studies were obtained every week during the first year and the same or bimonthly during the second year. Thereafter laboratory data were obtained at monthly intervals. Complete patient evaluation including intravenous pyelogram, creatinine clearance, renal scan, estimated renal plasma flow and routine laboratory data was obtained 6 months post transplantation and thereafter on a yearly basis.

Donor Patients. Patients considered for donor nephrectomy were interviewed by at least two members of the transplant team and selected after the appropriate laboratory and radiographic studies were obtained. The com-

TABLE 2. *Source of Donor Kidney*

Donor	No. Patients
Mother	28
Father	17
Brother	28
Sister	26
Daughter	1

TABLE 4. *Summary of Tissue Typing (100 Patients)*

Tissue Typing	No. Patients
A	15
B	24
C	34
D	27

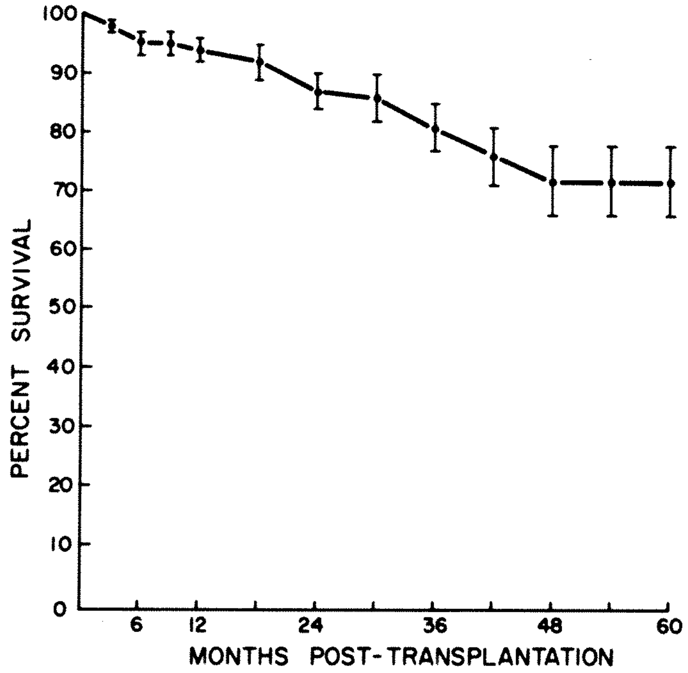


FIG. 1. Graft survival from living related donors with a minimum followup of one year. The number of patients at the beginning of the study is 100, 1 year—90, 2 years—61, 3 years—46, 4 years—22 and 5 years—10.

plete diagnostic evaluation was similar to that reported by Simmons.[19] The first three donor nephrectomy operations were performed by the transabdominal approach and the remaining 97 operations using the retroperitoneal flank approach with resection of the 11th or 12th rib. The left kidney was removed in 69 patients and the right kidney in 31. Three kidneys had double renal arteries and one had two renal veins of equal size. Seventy-seven per cent of the donor patients were between the age of 21 and 50. Two were under 20 and 21 were over the age of 50. All patients were seen at least twice postoperatively in the transplant clinic with yearly evaluation thereafter by either repeat clinic visits or by mail.

Results

Recipient Patients

Graft Survival. Seventy-three of the 100 patients are alive with a functioning allograft for an average followup period of 3 years and 2 months. The minimum followup was one year and the maximum 6 years and 2 months. Actuarial analysis of graft survival[3] revealed 94% to function at one year, 87% at 2 years, 81% at 3 years and 72% 4 and 5 years later (Fig. 1). Chronic rejection caused or contributed to graft failure in 13 recipients. Nine patients survived and were returned to dialysis. Two of the 4 retransplanted with related donor kidneys are included in this report. The other two received cadaveric allografts with excellent function and rehabilitation. One other patient had a hyperacute rejection and was returned to dialysis.

Patient Survival—Eighty-three per cent of all patients transplanted are alive as of July, 1975 and 17 died from 2½ months to 46 months post transplantation. Actuarial analysis of patient survival showed 93% to be alive at one year, 87% at 2 years, 84% at 3 years and 74% at 4 and 5 years (Fig. 2). No patients died from the operation or from complications resulting from the surgery.

Tissue Typing vs. Graft and Patient Survival. Histocompatibility matching of the 100 patients depicted in Table 4 was correlated with graft and patient survival. Only two of 39 patients classified as A or B matches have died (pulmonary embolism, trauma) and one has lost the graft to chronic rejection. In contrast 23 patients determined to be C or D matches have died (15 patients) or lost their grafts to chronic rejection (8 patients), (Figs. 4 and 5). Genotypic analysis of 98 patients revealed 27 of 30 patients sharing two haplotypes to be alive with functioning grafts. Two have died and one developed irreversible rejection with return to dialysis. Forty-seven of 68 patients sharing one haplotype are alive with functioning grafts. Fourteen recipients are dead and 7 are on dialysis after graft rejection.

Rejection Episodes vs. Tissue Typing. Forty-one patients never had a rejection episode, 54% of whom were A or B matches. Forty-one patients had one such rejec-

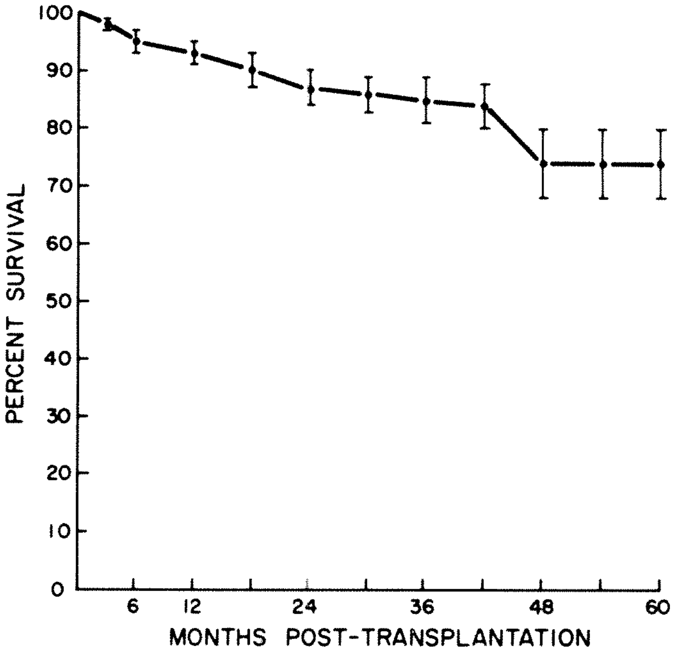
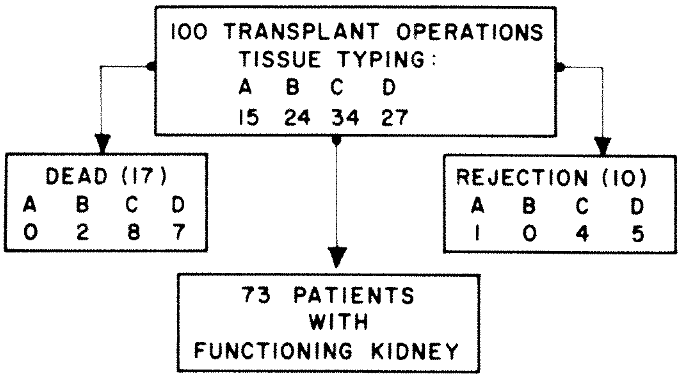


FIG. 2. Patient survival from living related donors with a minimum followup of one year. The number of patients at the beginning of the study is 100, 1 year—91, 2 years—64, 3 years—47, 4 years—22 and 5 years—10.



Rehabilitation

CLASS	A	B	C	D
EXCELLENT	10	13	13	6
GOOD	1	4	2	6
FAIR	2	3	6	3
POOR	1	2	1	0

FIG. 3. Rehabilitation post transplantation, average followup, 3 years and 2 months.

tion, with 33% A or B matches. Thirteen patients had two rejections and only 15% were reported as A or B matches. Five patients had three rejection crises, one of whom was an A match. The number of rejection episodes compared with the tissue typing revealed most patients with two or more rejections to be C or D matches (Table 5). The frequency and severity of rejection could not be correlated with the donor source of the kidney if the histocompatibility testing revealed a one haplotype match.

Five of 30 patients sharing both haplotypes developed acute rejection; one patient ultimately lost the graft due to chronic rejection. Fifty of 68 patients sharing one haplotype had one or more rejection episodes with 7 sustaining irreversible rejection. On the other hand 18 patients with one haplotype mismatch did not develop rejection and behaved similarly in graft survival and renal function to the group sharing two haplotypes. The number of patients not receiving ATG was inadequate for a statistical comparison with those individuals receiving ATG in terms of graft and patient survival and tissue typing.

Fatal Complications. Seventeen patients expired; 14 autopsies were done. Ten died from infection, 2 from trauma, 2 from myocardial infarction, one from pulmonary embolism and 2 on dialysis after graft rejection and transplant nephrectomy (Table 6). Eight of the patients had functioning grafts with a serum creatinine less than 2.0 mg/100 ml at the time of death. Eight of the 17 patients died in the first 12 post transplant months and only 5 after 25 months. *Pneumocystis carinii* caused the death of 4 patients, gram negative bacterial infection in 3, cytomegaloviremia in 2 and histoplasmosis in one. Only two of the patients who died shared two haplotypes, whereas the remaining 15 shared one haplotype.

Non-fatal complications. Thirty-three patients had no complications during or after transplantation. The remaining 67 patients have sustained a total of 98 complications or related illnesses since the operation (not including graft rejection), (Table 7). The most common early serious complication was related to the genitourinary tract although none resulted in graft loss. Eight of these were the result of technical errors leading to ureteral necrosis or vesicocutaneous fistula. The former complications required ureteropyeloplasty in three patients and pyelojejunocystotomy in one. Ureteral strictures involved the midportion of the ureter and were usually secondary to lymphocoeles. There were no strictures at the area of the ureterovesical anastomosis. Skeletal complications were the second most common cause of morbidity after transplantation. Eleven of the 14 patients with aseptic necrosis underwent prosthetic replacement of the femoral head with complete recovery and excellent rehabilitation. One patient also required bilateral total knee replacement with an excellent result. Infections complicated the post transplant course in 17 patients. Gram negative organisms usually involving the urinary tract were most common and occurred in 10 patients. Cryptococcal infections occurred in the lung and subcutaneous tissue in four patients. *Pneumocystis carinii* proven by lung biopsy was successfully treated by pentamidine in one instance. Serious viral infections occurred

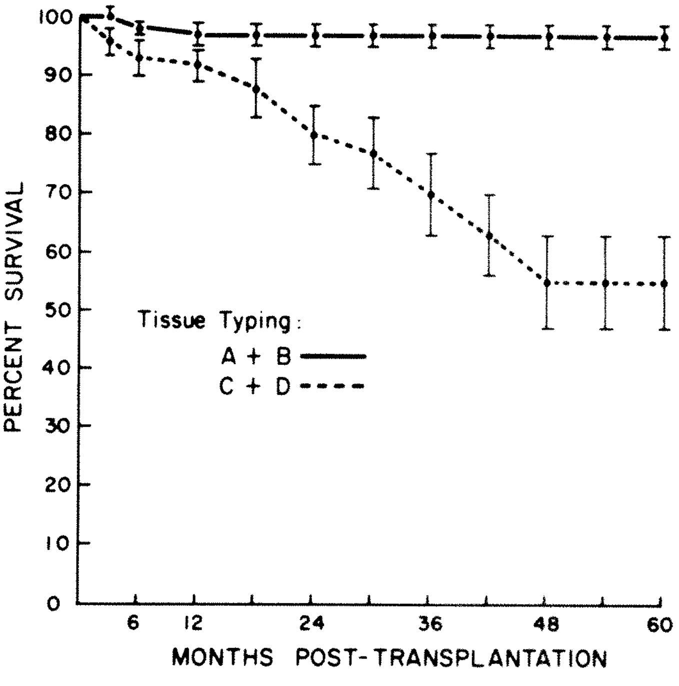


FIG. 4. Graft survival compared with tissue typing.

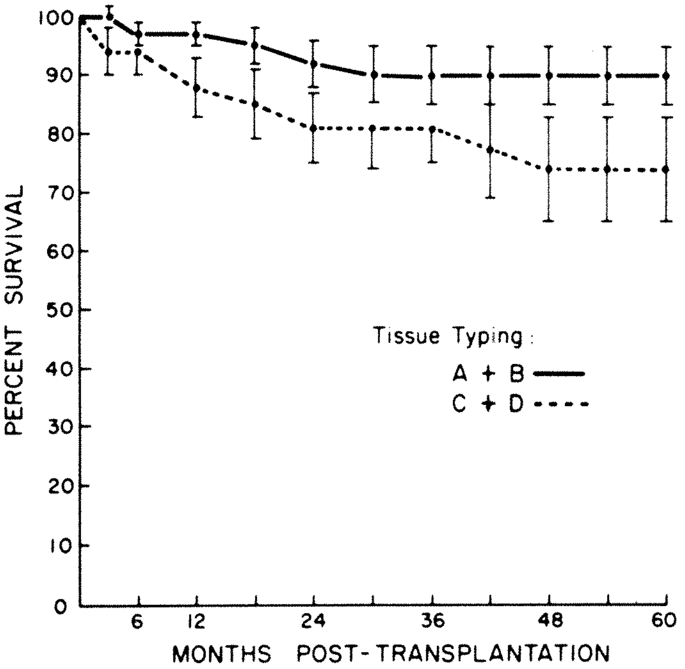


FIG. 5. Patient survival compared with tissue typing.

TABLE 5. *Rejection Episodes vs Tissue Typing*

		Tissue Typing			
No. Rejections	No. Patients	A	B	C	D
0	41	12	10	9	10
1	41	2	12	20	7
2	13	0	2	2	9
3	5	1	0	3	1
Total	100	15	24	34	27

in many patients all of which gradually subsided in time unless associated with pneumocystis. Diabetes developed in 11 patients all of whom were insulin dependent until the daily prednisone dosage was decreased to less than 20 mg/day. Gastroduodenal bleeding, intestinal obstruction, pneumonia, psychiatric depression and other complications occurred less frequently.

Rehabilitation. Seventy-three of the 100 allograft recipients are alive with functioning grafts. Ten other patients alive after retransplantation or who returned to hemodialysis following chronic rejection are not included. Forty-two of the 73 patients (58%) are considered to have excellent results. They lead a normal life without restrictions and their activities include fulltime work, students or housewives. Thirteen (18%) are classified as good results, and although some physical limitations exist, they have an active and useful life from the economic, social and psychologic aspect. Fourteen (19%) are moderately restricted in their daily activities and unable to work. Four (5%) are poor results with marked restrictions and are frequently hospitalized. Aseptic necrosis, chronic rejection, physical weakness, cataracts and psychiatric illness were the major causes of poor rehabilitation (See Fig. 3). In most instances the morbidity causing significant limitation of physical activity was the result of complications secondary to corticosteroid therapy. These problems rarely noted in the HLA identical patient were more common in the patient sharing one haplotype.

Renal function and immunosuppressive therapy. Ninety patients achieved the immediate onset of renal function which was maintained for at least the first 60 post transplant days. Ten patients required hemodialysis in the first post transplant month with ultimate recovery of kidney function in nine. In two patients prolonged ischemic intervals of 75 and 80 minutes required for completion of the vascular anastomoses contributed to the impaired renal function. A third patient developed acute tubular necrosis from intraoperative hypotension. Five of the 10 patients developed oliguria from acute rejection; 4 recovered after varying periods of dialysis. The remaining two patients had oliguria with suboptimal renal function for unknown reasons and eventually recovered.

The average serum creatinine for all patients with functioning grafts at one week was 2.0 mg/100 ml, 3 months 1.3 mg/100 ml and 6 months 1.4 mg/100 ml. Subsequent renal function at 5 yearly intervals included 1.5, 1.7, 1.9, 1.4 and 1.4 mg/100 ml.

All but two patients were maintained on azathioprine and prednisone in the postoperative period. These two had impaired hepatic function and jaundice secondary to cytomegalovirus with improvement after substituting cyclophosphamide for azathioprine. Patients receiving A and B matched kidneys were maintained on less prednisone (5–15 mg/day, average 10 mg/day) while C and D matched patients required more steroid therapy (12.5–20 mg/day, average 15 mg/day). Thirty of the 41 patients selected for alternate day prednisone therapy maintained stable renal function with an average prednisone dosage of 25 mg every other day (ranging from 10 mg to 47.5 mg). Nine patients developed chronic rejection during conversion; four of whom eventually lost their graft. Two

TABLE 6. *Cause of Death After Renal Transplantation*

Cause	No. Patients
Infection	10
Protozoal (4)	
Bacterial (3)	
Viral (2)	
Fungal (1)	
Accidental	2
Myocardial Infarction	2
Died on Dialysis	2
Pulmonary Embolism	1

TABLE 7. *Nonfatal Complications*

	Number of Complications	
Genitourinary		29
Ureteral necrosis	4	
Vesicocutaneous fistula	4	
Testicular torsion	1	
Lymphocoele	6	
Ureteral calculus	2	
Bladder stone	2	
Ureteral stricture or obstruction	4	
Epididymitis	6	
Skeletal		19
Aseptic necrosis	14	
Fractures	4	
Osteomyelitis	1	
Infection		17
Bacterial	10	
Fungal	4	
Viral	2	
Protozoal	1	
Endocrine		15
Diabetes	11	
Hyperthyroidism—toxic nodule	2	
Chronic pancreatitis	1	
Hyperparathyroidism	1	
Pulmonary		7
Pneumonia	5	
Embolism	1	
Tuberculosis	1	
Gastrointestinal		7
Intestinal obstruction	4	
Bleeding duodenal ulcer	3	
Vascular		2
Phlebitis	1	
Renal artery stenosis	1	
Psychiatric		2
Depression	2	
Total Number of Complications		98

additional patients had episodes of acute rejection successfully reversed with increased steroid therapy and subsequently maintained stable renal function.

Fertility. Two women became pregnant 6 months and 3 years post transplantation. Both delivered normal full-term children. One of the patients developed ureteral obstruction from a renal calculus immediately after delivery and required pyelolithotomy. Three male patients impregnated their wives post transplantation. Two had one child each and one had two children. One of the children was reported to have congenital heart disease of unknown type. All patients were maintained on azathioprine and prednisone and three had received ATG.

Malignancy. Four patients developed carcinoma of the skin. Three were of the squamous cell type and one had multiple basal cell carcinomas. All have responded well to excision without recurrence.

Donor Patients. Ninety-six donors were known to be alive and well as of July 31, 1975. One donor died from a car accident and two were lost to followup. The fourth donor developed chronic renal disease secondary to a collagen disorder with slightly impaired kidney function. The average hospital stay after donor nephrectomy was 7.8 days ranging from 5 to 21. The list of complications encountered are noted in Table 8. Urinary tract infection occurred in 20 patients and required antibiotic treatment. The serum creatinine after nephrectomy at the time of hospital discharge was less than 1.4 mg/100 ml in 65 patients, between 1.5 and 2.0 mg/100 ml in 27 patients and greater than 2.0 mg/100 ml in one patient. Although only 5 patients received blood transfusions during the operation the post nephrectomy discharge hematocrit was less than 30% in 40 patients. The incidence of complications in the 21 patients over the age of 51 was no greater than those encountered in the younger age group.

A detailed interview was conducted in 74 of the 100 donors from 9 months to 4 years post transplantation. Two patients had some concern about whether or not the previous donation was the proper decision. Neither felt pressured by physicians or family to donate but subsequently wondered about the use of cadaver kidneys as a substitute for living related donor transplantation. Two patients claimed to be unable to work after donor nephrectomy and are on disability. Two patients have had multiple hospital admissions for urinary tract infections and incisional pain. One other patient had repair of an incisional hernia.

Discussion

A realistic patient management program for chronic renal failure by renal transplantation requires careful analysis of multiple factors if the results are to be compared with those achieved by long-term hemodialysis. Minimal morbidity and mortality for the donor patient is implicit in the use of living related donor kidneys. In addition the expected survival of the recipient patient must be equal to or greater than that obtained with long-term hemodialysis if the inherent risks of the procedure are to be justified. The results presented here confirm the previous observations that donor mortality and morbidity were indeed minimal,[2,13,20] with excellent graft and patient survival.

TABLE 8. *Complications of Donor Nephrectomy*

Type of Complication	No. Patients
Urinary tract infection	20
Pneumothorax	
Treated	2
Untreated	9
Blood transfusions	5
Wound infection	3
Atelectasis	2
Incisional hernia	1

The overall mortality rate of 17% for the recipient patient during an average followup period of 3 years and 2 months compares favorably with other reports.[9,11,22] Since no patients died during the first 60 days after transplantation the operative risk must be considered small. Patients receiving A and B matched kidneys generally had a better graft and patient survival. Only two patients in these groups expired and both had normal renal function. In contrast 15 of 61 patients receiving C or D matched kidneys died. The most common cause of death was from infection secondary to gram negative septicemia, pneumocystis, cytomegaloviremia and histoplasmosis. The incidence of these infections increased if the recipient sustained one or more rejection episodes and was probably related to the increased total steroid dose required for anti-rejection therapy. The morbidity caused by nonfatal complications was also greater in patients receiving C or D matched kidneys, reflecting the increased number of rejection episodes. Similar findings were recently reported in a review of fungal infections in transplant patients.[7]

Graft survival by actuarial analysis supported the previous observation that patients receiving kidneys determined to be HLA identical or without a major mismatch (A or B) have a much better prognosis in duration of survival and quality of function.[24] In our experience only one of 39 such patients lost their kidney to rejection. Patients transplanted with C or D matched kidneys, i.e. one haplotype mismatch had a much less favorable graft survival and is similar to that reported previously by Kountz.[9]

Nonfatal complications were a source of concern. Some of these were minor but when related to the genitourinary tract were often serious. The relatively high incidence of these complications in our experience primarily occurred during the first 50 operations and have become rare as surgical technique improved. Urologic complications are especially serious in that perinephric space infection may ensue causing transplant site sepsis. Early diagnosis may be difficult since urologic complications are often similar to acute rejection causing delay in surgical intervention. However, once the diagnosis is established aggressive surgical intervention has been most effective in the management of these complications in the immediate post transplant course.[21] Lymphoceles occurred between 3 and 15 months after transplantation causing impaired renal function secondary to hydronephrosis and all responded to simple drainage. Skeletal complications most specifically aseptic necrosis occurred more commonly in patients receiving C or D matched kidneys requiring large doses of corticosteroid therapy[4] and occurs less often when prednisone was administered on an alternate day basis.[16] Pancreatitis,[12,25] septicemia[1] and wound infection,[15] diabetes,[14] pulmonary complications[18] and gastrointestinal bleeding[11] were all serious complications which occurred with varying frequency and morbidity.

Patient rehabilitation in part reflects the degree of histoincompatibility between the donor and recipient.[24] Fifty-five (76%) of the 73 patients alive with functioning grafts have good to excellent results and lead an active and useful life with stable renal function (See Fig. 3). Although a large percentage of these patients received A or B matched kidneys there were also a significant number of individuals transplanted with C and D matched organs. Therefore, some less well matched kidneys can maintain excellent renal function allowing the patient to return to an active and useful life. These grafts for reasons unknown have few or no rejection crises and behave in a manner indistinguishable from better matched kidneys. This is an important consideration because in our experience much of the morbidity and mortality in related living donor transplantation occurs in the patient population with C and D matched grafts sustaining one or more rejection crises. Methods of separating the more successful from the less successful recipient in this group would clearly improve the overall graft and patient survival curve toward that found in the A and B matched recipient noted in Figs. 4 and 5.

Decisions involving the selection of long-term dialysis versus renal transplantation for a given patient with chronic renal failure can be made with increasing confidence. Patients between the ages of 15 and 45 without gastrointestinal, cardiac or cerebrovascular disease and are able to receive a kidney from a relative should have a favorable prognosis.[17] If the patient has an HLA identical match then the results for long-term patient survival, graft function and overall rehabilitation are excellent.[9,22] Prolonged renal function has been observed once patients survive the early postoperative period and confirms the durability of the transplanted kidney.[22] In some instances perhaps individuals who are in the high risk category[17] may be better managed by long-term dialysis as opposed to cadaveric renal transplantation.[10]

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DISCUSSION

DR. JOHN C. MCDONALD (New Orleans): This has been a superb presentation by Dr. Diethelm, outlining his experience with living related donor grafts. His manuscript is certainly exemplary for its clarity and its completeness, and the results which he has obtained are certainly comparable to those that can be presented by any other major transplantation group.

The results, while they are good, need improvement in several areas. The surgical mortality is small, but the surgical morbidity is high. Almost all of this morbidity is ultimately related to tissue incompatibility. Both septic and technical complications relate to decreased host resistance or defective wound healing, induced by high dose immunosuppressive therapy in incompatible recipients. Grafts which are HL-A compatible certainly yield good long-term results, which are much better than those of HL-A incompatible grafts, as demonstrated in this paper. However, HL-A compatibility alone does not ensure success. In this present series, 17 patients with no demonstrable HL-A incompatibility had rejection episodes, and at least one graft was lost. This experience is similar to that of a number of other groups. Certainly, there is now abundant evidence that other compatibility loci exist in addition to the HL-A locus.

The Tulane laboratory has been studying a heterophile system which we have called the HT-A locus for the past several years, and due to some recent insights into this locus, we can now present some data for the first time relative to the biologic significance of this locus. I would like to show one slide.

(Slide) This shows the cumulative effect of both loci. The HT-A and HL-A compatible groups yield uniform success at 12 months, while HT-A and HL-A incompatibility yields almost uniform failure, with only 33% of allografts functioning at the end of a year.

Particularly important is the HL-A compatible but heterophile incompatible group of grafts, of which there are nine patients, seven of whom had severe rejection episodes, and two grafts lost. This group shows that it is now possible to select out those previously unexplained failures in HT-A compatible groups.

If this type of work is to ensure improved transplantation results, it must include grafts from cadaver donors, of which a third of the eighty patients in this graph are.

In this regard, Dr. Diethelm has made a somewhat interesting statement in his paper, which apparently reflects a substantial amount of pessimism with regard to cadaver grafting. I wonder whether he would be willing to expand upon that view in his closing.

DR. JOHN L SAWYERS (Nashville): The transplant program at the Vanderbilt University Medical Center, which is now directed by Dr. Robert Richie, has been involved mainly with the use of cadaver donor kidneys. However, in the past five years Dr. Richie and I have performed 35 kidney transplants from living related donors. Initially, it was our policy to use only four-antigen sibling donors. During the past year we have identified some three-antigen matches, and these have been utilized also.

Our results are consistent with those of Dr. Diethelm; that is, in the better matched living related donors, the graft survival rate is much better and mortality and morbidity are much lower because less immunosuppression is required.

(Slide) This shows that there are 20 patients who have had transplants, ranging from one to five years. All of these grafts were four-antigen matches, with one exception, which was a three-antigen match; and this graft was lost to rejection in the first month posttransplant. The remaining grafts are functioning well. There was one death in an individual two years posttransplant from a cerebrovascular accident. His kidney graft was removed and retransplanted.

We have transplanted one two-antigen match from parent to child, and this was rejected in the early posttransplant period. The remaining 14 grafts which have been done within the past year are all functioning well.

At present it is our policy to do only three- or four-antigen living related donor grafts, and to do three- or four-antigen cadaver donor grafts. Dr. Richie has performed a total of 21 four-antigen cadaver grafts with a one-year graft survival rate of 70%. He has also performed a total of ninety-one three-antigen cadaver renal allografts with a one-year graft survival rate of 65%. This is in contrast to the zero-, one-, and two-antigen cadaver graft survival rates, which are below a 40% survival rate at one year.

We agree with Dr. Diethelm that improved patient selection, and especially selection of carefully matched donors by tissue typing, are important factors for successful results of renal transplantation, not only for living related donors, but also for cadaver donor grafts.

Dr. Arnold G. Diethelm (Closing discussion): I feel strongly that cadaveric renal transplantation is an important part of a transplantation program. In this regard, we have an active cadaveric program which is increasing yearly in numbers.

I think Dr. McDonald has pointed out a very crucial point, and that is that patients who are a one-haplotype mismatch—half of those patients do very well, and half do poorly. If we could separate out the group that will have stable graft function in advance, then we would not have to determine the poor results through graft failure. Perhaps his methods of tissue typing will help us in that area.

I agree with Dr. Sawyers' comments regarding the use of tissue typing. We are continuing to utilize the one-haplotype mismatch with the C and D match patient, recognizing the comments that I just made. Tissue typing with cadaveric grafts is difficult to interpret, and the data is not entirely clear. The information from Europe would lead us to believe that tissue typing—specifically, three- and four-antigen matches—have better graft survival. The same data from the United States would lead us to believe that it's not so helpful. I think what's more important is that a single group, such as the Vanderbilt group, carefully study a small series of patients. And if their data continues to be encouraging, then that may mean much more than large series of pooled data.

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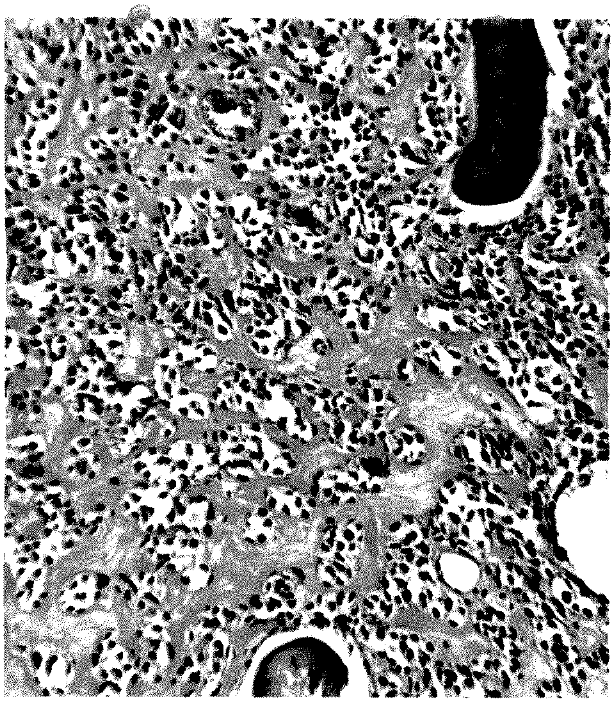

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3. Dosage should be reduced in patients with impaired hepatic function.
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CLINICAL PHARMACOLOGY

Though not completely elucidated, the mechanism of action of doxorubicin is related to its ability to bind to DNA and inhibit nucleic acid synthesis. Cell culture studies have demonstrated rapid cell penetration and perinucleolar chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, mutagenesis and chromosomal aberrations. Animal studies have shown activity in a spectrum of experimental tumors, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including cardiac toxicity in rabbits, myelosuppression in all species and atrophy to testes in rats and dogs. Teratology studies, though not showing a definite increase in specific or nonspecific malformations, indicate a moderate interference with the viability of embryos and fetuses.

Pharmacokinetic studies show the intravenous administration of normal or radiolabeled Adriamycin (doxorubicin hydrochloride) for injection is followed by rapid plasma clearance and significant tissue binding. Urinary excretion, as determined by fluorimetric methods, accounts for approximately 4-5% of the administered dose in five days. Biliary excretion represents the major excretion route, 40-50% of the administered dose being recovered in the bile or the feces in seven days. Impairment of liver function results in slower excretion, and, consequently, increased retention and accumulation in plasma and tissues. Adriamycin does not cross the blood-brain barrier.

INDICATIONS

Adriamycin has been used successfully to produce regression in neoplastic conditions such as: acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, bronchogenic (lung) carcinoma, thyroid carcinoma and lymphomas of both Hodgkin and non-Hodgkin types. A number of other solid tumors have also shown some responsiveness but in numbers too limited to justify specific recommendation. Studies to date have shown malignant melanoma, kidney carcinoma, large bowel carcinoma, brain tumors and metastases to the central nervous system not to be significantly responsive to Adriamycin therapy.

CONTRAINDICATIONS

Adriamycin therapy should not be started in patients who have marked myelosuppression induced by previous treatment with other antiblastic agents or by radiotherapy. Conclusive data are not available on pre-existing heart disease as a co-factor of increased risk of Adriamycin-induced cardiac toxicity. Preliminary data suggest that in such cases cardiac toxicity may occur at doses lower than the recommended cumulative limit. It is therefore not recommended to start Adriamycin in such cases. Adriamycin treatment is contraindicated in patients who received previous treatment with complete cumulative doses of Adriamycin and daunorubicin.

WARNINGS

Special attention must be given to the cardiac toxicity exhibited by Adriamycin. Although uncommon, acute left ventricular failure has occurred, particularly in patients who have received total dosage of the drug exceeding the currently recommended limit of 550 mg/m² of body surface. This limit appears to be lower (400 mg/m²) in children who received radiotherapy to the mediastinal area. The total dose of Adriamycin administered to the individual patient should also take into account any previous or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide or related compounds such as daunorubicin. It should be noted that the cardiac failure may also occur several weeks after administration of the drug and is often not favorably affected by presently known medical or physical therapy for cardiac support. Early clinical diagnosis of drug-induced heart failure appears to be essential for successful treatment with digitalis, diuretics, low salt diet and bed rest. Severe cardiac toxicity may occur precipitously without antecedent EKG changes. Baseline EKG and periodic follow-up EKG during, and immediately after, active drug therapy is an advisable precaution. Transient EKG changes, such as T-wave flattening, S-T depression, and arrhythmias are presently not considered indications for suspension of Adriamycin therapy. A reduction in the voltage of the QRS wave is presently considered more specifically predictive for cardiac toxicity. If this occurs, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

There is a high incidence of bone marrow depression, primarily of leukocytes, requiring careful hematological monitoring. With the recommended dosage schedule, leukopenia is usually transient, reaching its nadir at 10-14 days after treatment with recovery usually occurring by the 21st day. White blood cell counts as low as 1000/mm³ are to be expected during treatment with appropriate doses of Adriamycin. Red blood cell and platelet levels should also be monitored since they may also be depressed. Hematologic toxicity may require dose reduction or suspension or delay of Adriamycin therapy. Persistent severe myelosuppression may result in superinfection or hemorrhage.

Toxicity to recommended doses of Adriamycin is enhanced by hepatic impairment, therefore, prior to the individual dosing, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase, bilirubin, and BSP (see DOSAGE AND ADMINISTRATION).

On intravenous administration of Adriamycin, a stinging or burning sensation signifies a small degree of extravasation and even if blood return from aspiration of the infusion needle is good, the injection or infusion should be immediately terminated and restarted in another vein.

PRECAUTIONS

Initial treatment with Adriamycin requires close observation of the patient and extensive laboratory monitoring. It is recommended, therefore, that patients be hospitalized at least during the first phase of the treatment.

There is no adequate information on whether this drug may adversely affect fertility in human males or females, or have a teratogenic potential or other adverse effects on the fetus. Experimental data, however, suggest that Adriamycin may reduce the viability of the fetuses, therefore the benefits to the pregnant patient should be weighed against the potential toxicity to fetus and embryo. Adriamycin and related compounds have also been shown to have mutagenic and carcinogenic properties when tested in experimental models.

Adriamycin imparts a red coloration to the urine for 1-2 days after administration and patients should be advised to expect this during active therapy.

Adriamycin is not an antimicrobial agent.

ADVERSE REACTIONS

Dose-limiting toxicities of therapy are myelosuppression and cardiotoxicity (see WARNINGS). Other reactions reported are:

Cutaneous — Reversible complete alopecia occurs in most cases. Hyperpigmentation of nailbeds and dermal creases, primarily in children in a few cases. Recall of skin reaction due to prior radiotherapy has occurred with Adriamycin administration.

Gastrointestinal — Acute nausea and vomiting occurs frequently and may be severe. This may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) may occur 5-10 days after administration. The effect may be severe leading to ulceration and represent a site of origin for severe infections. The incidence and severity of mucositis is greater with the 3 successive daily dosage regimen. Anorexia and diarrhea have been occasionally reported.

Vascular — Phlebosclerosis has been reported especially when small veins are used or a single vein is used for repeated administration. Facial flushing may occur if the injection is given too rapidly.

Local — Severe cellulitis, vesication and tissue necrosis will occur if Adriamycin is extravasated during administration. Erythematous streaking along the vein proximal to the site of the injection has been reported.

Hypersensitivity — Fever, chills and urticaria have been reported occasionally. Anaphylaxis may occur. A case of apparent cross sensitivity to lincomycin has been reported.

Other — Conjunctivitis and lacrimation occur rarely.

DOSAGE AND ADMINISTRATION

The recommended dosage schedule is 60-75 mg/square meter of body surface, as a single intravenous injection administered at 21-day intervals. The lower dose should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. An alternative dose schedule is 30 mg/square meter of body surface on each of three successive days repeated every 4 weeks. If hepatic function is impaired, Adriamycin dosage must be reduced according to the following table:

Serum Bilirubin Levels	BSP Retention	Recommended Dose
1.2 – 3.0 mg %	9 – 15%	½ normal dose
>3 mg %	>15%	¼ normal dose

Preparation of Solution: Adriamycin should be reconstituted with Sodium Chloride Injection U.S.P. as indicated in the Dilution Table.

Dilution Table		
Vial Size	Quantity of Diluent to be Added	Approximate Concentration
10 mg	5 ml	2 mg/ml
50 mg	25 ml	2 mg/ml

If Adriamycin powder or solution contacts the skin or mucosae, wash thoroughly with soap and water.

After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 24 hours at room temperature and 48 hours under refrigeration (4-10°C). It should be protected from exposure to sunlight and any unused solution should be discarded.

It is recommended that Adriamycin be administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection U.S.P. or five percent (5%) Dextrose Injection U.S.P. This procedure will reduce likelihood of extravasation and consequent tissue damage.

Adriamycin should not be mixed with heparin since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Until specific compatibility data is available, it is not recommended that Adriamycin be mixed with other drugs.

Adriamycin has been used in combination with other approved chemotherapeutic agents. Though evidence is available that at least in some types of neoplastic disease combination chemotherapy is superior to single agents, the benefits and risks of such therapy have not yet been fully elucidated.

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Versatile, this single retractor permits complete visualization of any abdominal operating field without assistants . . . allows greater working area and freedom of movement for efficient operating teamwork.

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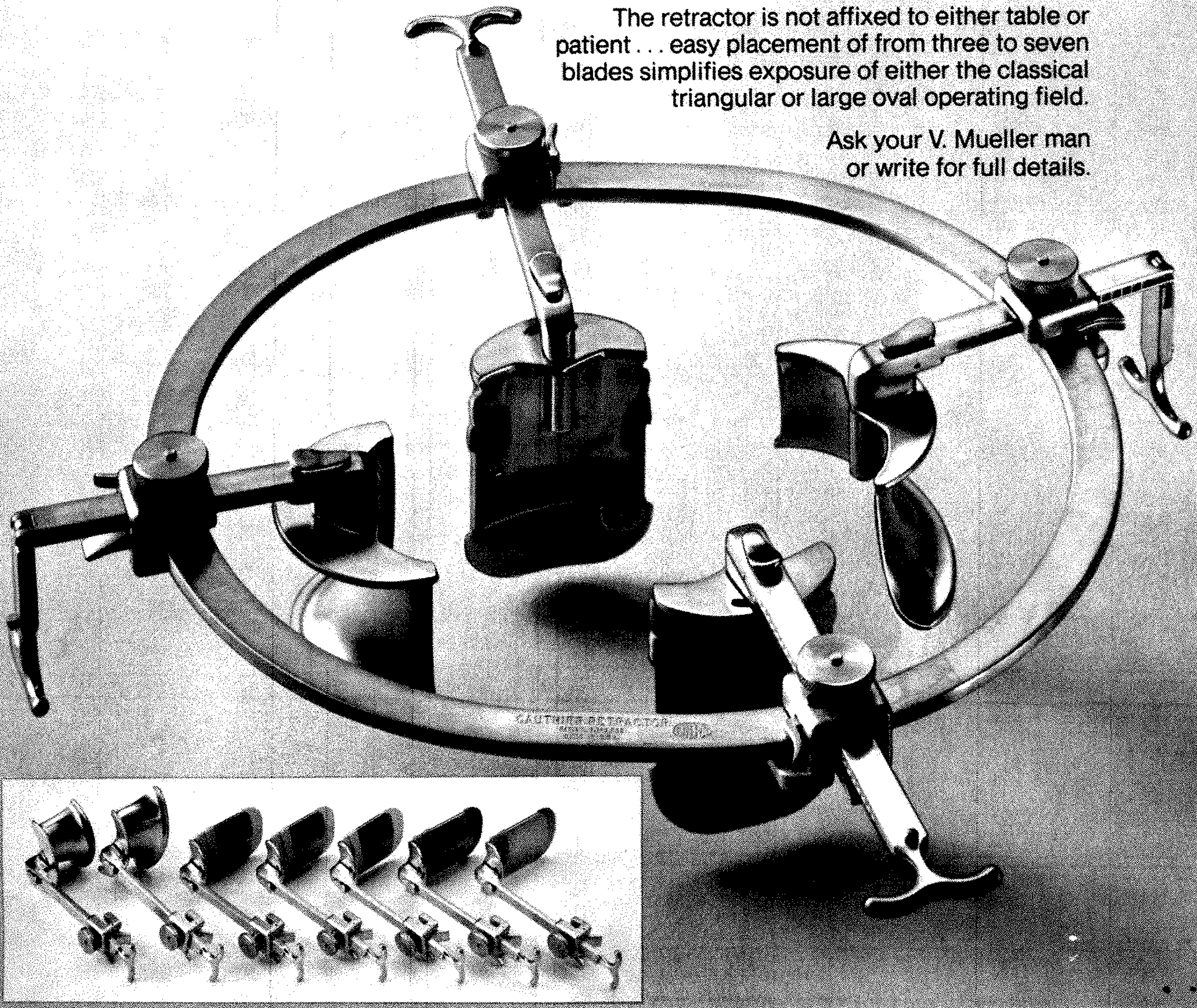

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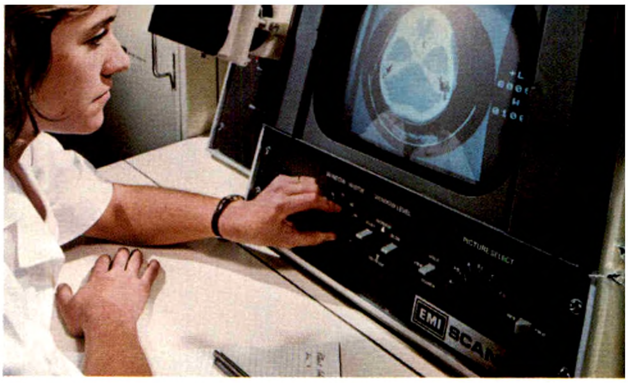
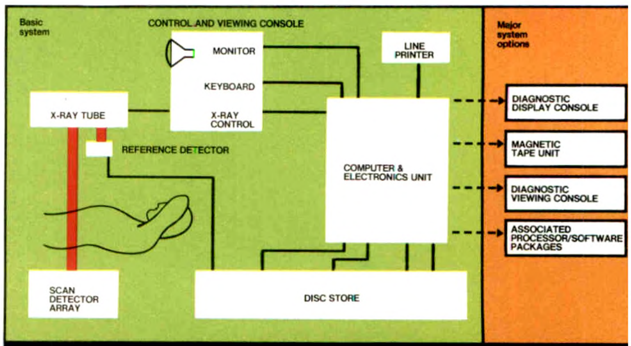
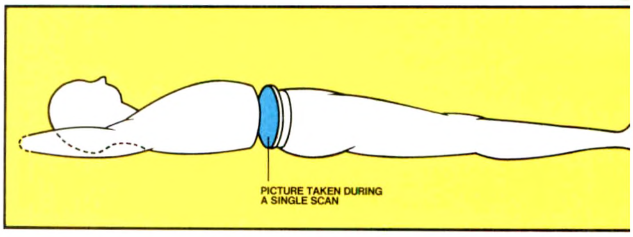




The EMI-Scanner CT5005 can resolve picture elements as small as 0.75 mm x 0.75 mm.



6-216

The EMI CT5005 head and body scanner provides

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Like its companion system—the EMI CT1010 Neuro C.T. Scanner—our new EMI-Scanner CT5005 Advanced General Diagnostic C.T. System is based on fully proven technology that has established EMI as the unrivaled world leader in computerized tomographic scanning. This new head and body scanning system combines the capability for exceptional resolution, definition and accuracy in the pictures produced, a very fast scanning cycle, unusually powerful computing capability and other advanced features that contribute to ease-of-operation and efficient patient handling. The CT5005 General Diagnostic System can be tailored by selection of the appropriate choice of peripherals and software packages to meet specific clinical needs. Obviously, for the radiologist and referring physician alike, the quality of the scan picture itself is the final proof of any CT system's performance. The EMI-Scanner System has met this test in hundreds of institutions. It is the world's only fully proven scanner system. For information, call us or write.

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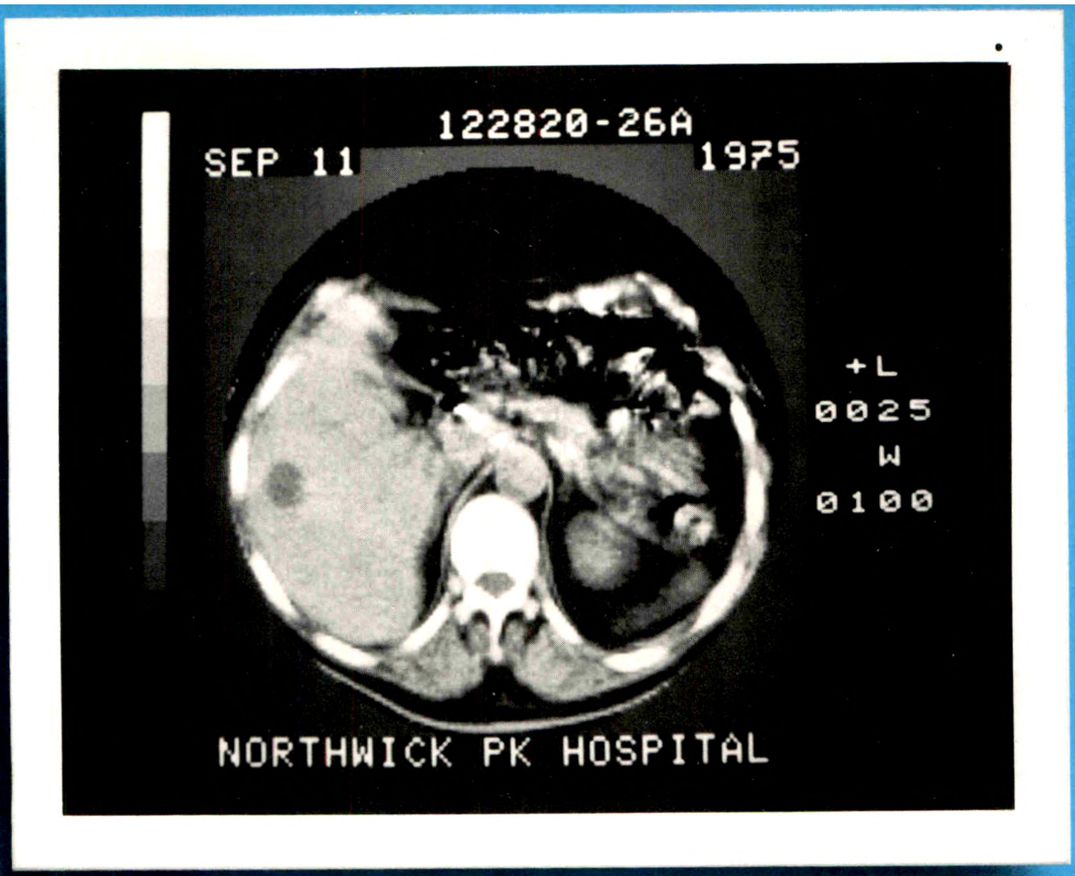

EMI-SCAN taken at the level of the 12th thoracic vertebra. The dark area of low absorption is a metastasis from a prostatic carcinoma. This lesion was not suspected until shown on the EMI-SCAN.

6-220

Superior diagnostic information in every EMI-SCAN:

A metastatic lesion at T12

The EMI-Scanner CT5005 Advanced General Diagnostic C.T. System allows accurate visualization of detailed tissue structures that are extremely difficult to investigate with alternative techniques. Based on thoroughly proven EMI technology, this new head and body scanner has also demonstrated improved diagnostic accuracy in areas where current methods have been regarded as satisfactory. The CT5005 employs a rapid scanning cycle to record more than 300,000 X-ray readings per scan. Exceptionally powerful data processing capability ensures that the full potential of the information in the photon beam is realized in the patient's scan pictures. In the high-resolution format, picture elements 0.75 mm x 0.75 mm can be resolved. The diagnostic precision of EMI-SCAN pictures is proving a major benefit in examining conditions such as metastases in organs including the liver, pancreas, and kidneys, and in studies of the skull, retro-sternal area, inferior angles of the lungs, spleen and spinal canal. For information, call us or write.

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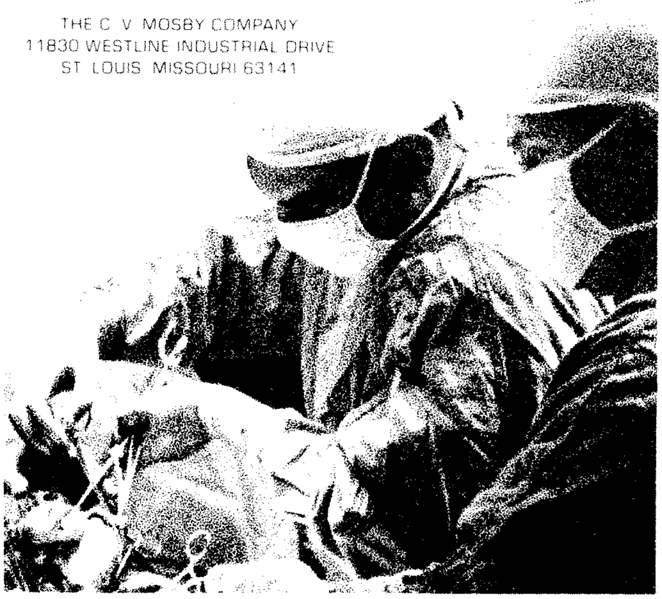

DARVOCET-N® 100

propoxyphene napsylate with acetaminophen

Indication: For the relief of mild to moderate pain, either alone or accompanied by fever.

Contraindications: Hypersensitivity to propoxyphene or to acetaminophen.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions. [011375]

DARVON® COMPOUND-65

propoxyphene hydrochloride, aspirin, phenacetin, and caffeine

Indication: For the relief of mild to moderate pain.

Contraindication: Hypersensitivity to propoxyphene, aspirin, phenacetin, or caffeine.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine.

The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Phenacetin has been reported to damage the kidneys when taken in large amounts for a long time.

Salicylates may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions. [011375]

Lilly

Additional information available to the profession on request.

Eli Lilly and Company, Inc.
Indianapolis, Indiana 46206

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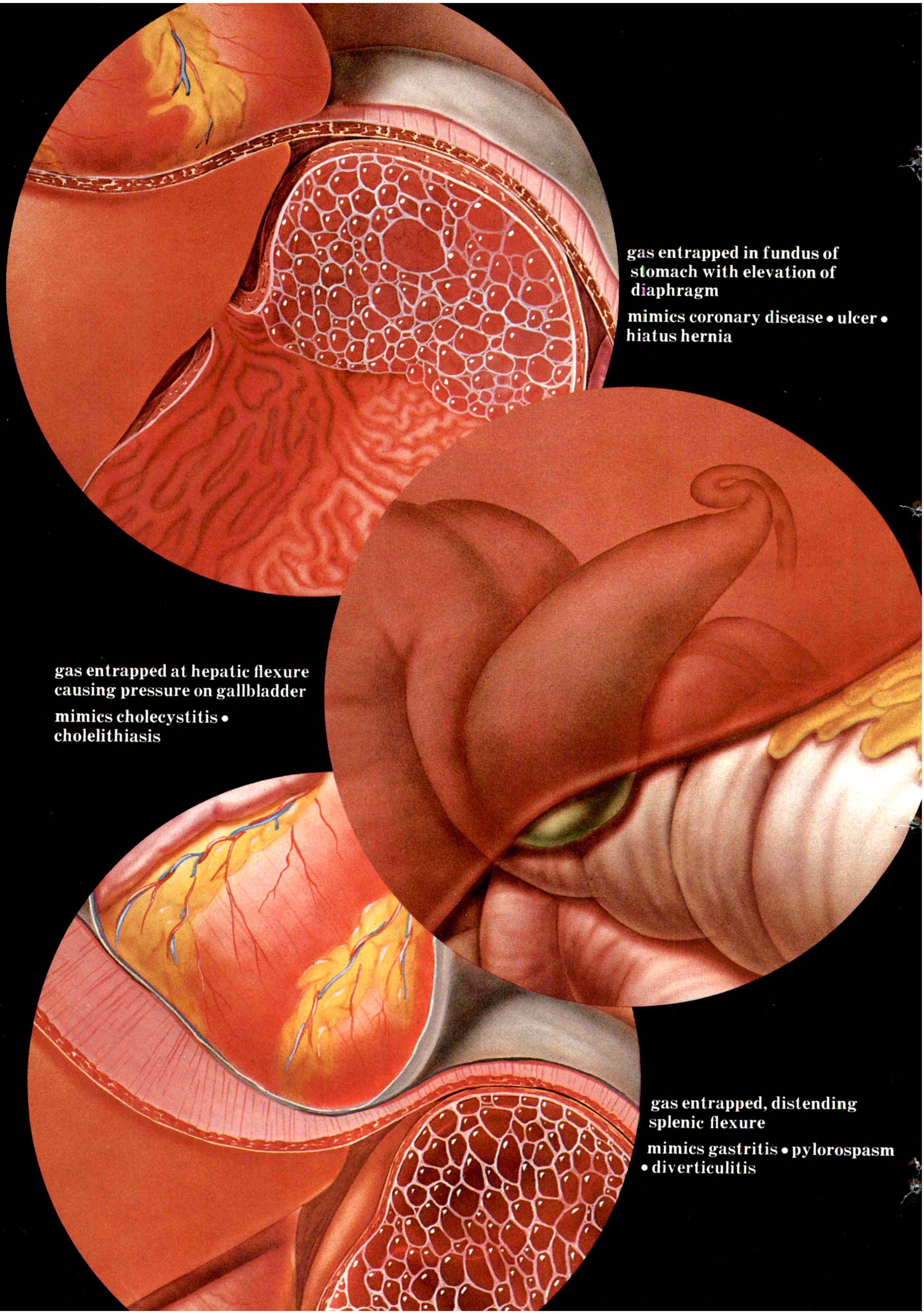
Relief from her postsurgical pain

Darvocet-N® 100
100 mg. propoxyphene napsylate and
650 mg. acetaminophen
contains no aspirin

Darvon® Compound-65
65 mg. propoxyphene hydrochloride, 227 mg. aspirin,
162 mg. phenacetin, and 32.4 mg. caffeine
contains aspirin

for mild to
moderate pain

See summary of prescribing information on adjoining page.



gas entrapped in fundus of stomach with elevation of diaphragm

mimics coronary disease • ulcer • hiatus hernia

gas entrapped at hepatic flexure causing pressure on gallbladder

mimics cholecystitis • cholelithiasis

gas entrapped, distending splenic flexure

mimics gastritis • pylorospasm • diverticulitis

Organic pain and

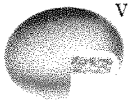
The Gas Masquerade

Organic pain due to entrapped gas relieved by

Phazyme®

The organic pain caused by gas entrapped in the GI tract can be just as severe as that of the diseases it may originally have suggested. When the masquerade is over, Phazyme provides specific dual-phase action to relieve the real pain behind the false alarm your diagnostic workup has excluded.

For immediate relief, outer layer delivers 20 mg. of specially-activated simethicone directly to the stomach for rapid dispersion of entrapped gas.



For continued relief, protected inner core delivers 40 mg. of specially-activated simethicone to relieve gas distress throughout the lower GI tract. The core also releases 240 mg. of pancreatin directly to the small intestine to enhance normal digestion.

And PHAZYME is safe... no systemic effects ... no untoward reactions... no contraindications other than known allergy to an ingredient.

and when the aerophagia of chronic anxiety results in gas pain

Phazyme®-PB Tablets

ⓒⅣ containing ¼ grain phenobarbital
(Warning: may be habit forming.)

Formula: The outer layer releases in the stomach: specially-activated simethicone 20 mg. and phenobarbital (WARNING: May be habit forming.) 15 mg. The enteric coated core releases in the small intestine: pancreatin, N.F. 240 mg., and specially-activated simethicone 40 mg.
Contraindications: Sensitivity to barbiturates or known allergy to an ingredient.
Phazyme is available in bottles of 50, 100, and 1,000 pink tablets.
Phazyme-PB is available in bottles of 100 and 1,000 yellow tablets.

Reed & Carnrick/Kenilworth, N.J. 07033

Upjohn

Anaerobic GI flora–site specific

The gastrointestinal tract of man contains an abundance of microorganisms composed predominantly of anaerobic bacteria. The geographic location of these bacteria in the intestine may explain the different rates of infectious complications associated with injuries to different parts of the gastrointestinal tract. Soilage from the upper portion of the small bowel is usually associated with a lower rate of infection than from the lower small bowel and colon.

Intra-abdominal infections: Intra-abdominal infections may complicate penetrating abdominal wounds, particularly when the integrity of the bowel has been compromised. Such complications are frequently associated with trauma resulting from automobile accidents or criminal violence (such as gunshot wounds or stabbings). Anaerobic infections may occur as postsurgical complications. Peritonitis and abscess formation may cause particular problems. Intra-abdominal infections may also occur when bowel tissue becomes necrotic or nonviable as in cases of vascular compromise, embolic disease, obstruction, strangulation, toxic dilatation, and similar conditions characterized by tissue anoxia.

Appropriate therapy for the infectious complications is often a concern of many physicians.

...and how to manage them: The initiation of antibiotic therapy, particularly when peritonitis exists, may be a matter of immediate importance. In such emergency situations, the surgeon's selection of an antibiotic is frequently made on the basis of scant etiologic evidence. However, his knowledge of the specific normal flora in a given area of the bowel and how the flora can be altered by certain pathologic conditions will aid him greatly in his antibiotic selection.

Therapy which must be initiated presumptively may be chosen discriminatively: While inspection of Gram-stained specimens may prove useful, and cultures from the infection site will eventually provide valuable diagnostic information for the surgeon, the best clue to immediate antibiotic therapy may be the location of the infection. In the normal healthy adult, there is well-defined colonization by specific microorganisms in specific sites of the gastrointestinal tract. Thus a guide to the *normal* inhabitants of various areas may be helpful in suggesting the proper therapeutic agent.

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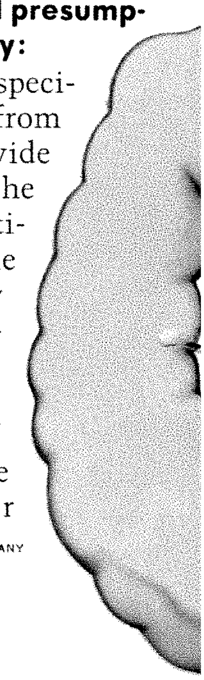
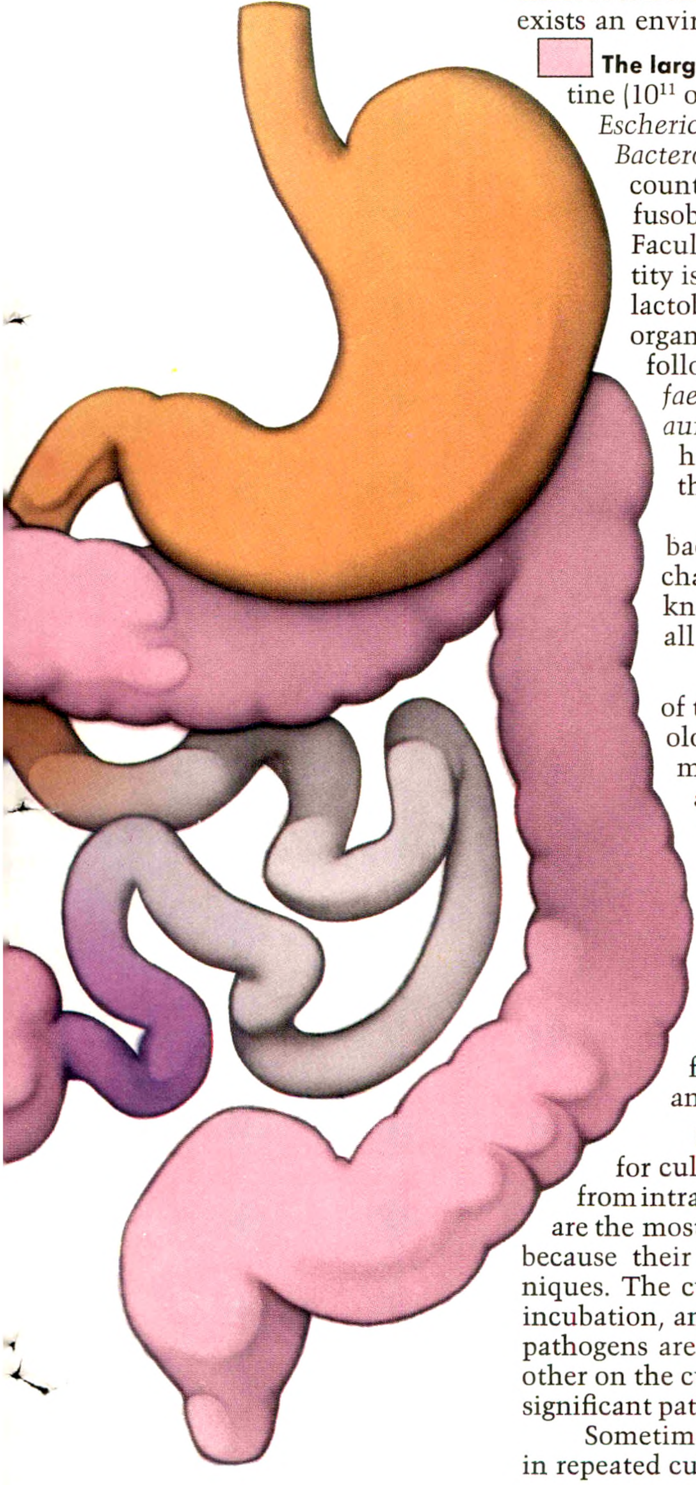


Guide to the normal adult intestinal microflora

🟧 **The stomach, and proximal and middle small bowel:** Here facultative enterococci, lactobacilli and anaerobes (originating in the oral cavity) exist in a concentration of 10^5 or less organisms per ml of contents. *Bacteroides fragilis* is virtually absent. Gastric acidity in this area limits the growth of many bacteria; therefore, most of the organisms are acid-resistant. In the middle portion of the small bowel there is sparse indigenous bacterial colonization, largely because of pronounced motility of this region.

🟪 **The distal small bowel:** In the ileum, enterococci and lactobacilli are seen in approximately the same quantities that occur in the stomach and duodenum. Coliforms are also observed—as are obligate anaerobes. *Bacteroides fragilis* and other fecal anaerobes first appear at this level. In fact, aerobic and anaerobic bacteria exist here in roughly equal proportions. The ileocecal valve, if functioning properly, provides a barrier against colonization by fecal anaerobes from the large bowel into this area. Beyond the ileocecal valve there exists an environment best suited to the proliferation of obligate anaerobes.



🟥 **The large bowel:** Anaerobic microorganisms predominate the large intestine (10^{11} organisms per gram of contents). Obligate anaerobes outnumber *Escherichia coli* 1,000 to 10,000 to one in the large intestine, and *Bacteroides fragilis* is the anaerobic organism most frequently encountered. Other anaerobes, such as peptostreptococci, clostridia, fusobacteria, and eubacteria are also seen although not so profusely. Facultative aerobes are in the decided minority here, but their quantity is no less than elsewhere in the intestinal tract. Enterococci and lactobacilli are each present in concentrations of about 10^6 to 10^8 organisms per gram of contents. *Escherichia coli* is most common, followed by enterococci *(Streptococcus faecalis* and *Streptococcus faecium),* proteus, pseudomonas, and klebsiella. *Staphylococcus aureus* and *Candida albicans* are also present in the large bowel of healthy, normal individuals. The pathogenic potential of each of these microorganisms should never be overlooked.

Because the large bowel contains many different species of bacteria, disease or trauma in this area may present a special challenge. Accordingly, it is important to remember that no known single agent has proved to be uniformly effective against all of these organisms.

Variations in the normal microflora: The normal microflora of the intestinal tract may be substantially altered in certain pathological conditions. These alterations depend upon the patient's medical history and the nature of his present illness. If, for example, the patient has achlorhydria, tissue ischemia, reduced intestinal motility, blind loop syndrome or stasis, or has had previous antibiotic therapy or bowel surgery, significant changes in the microflora of the bowel may be observed. When gastric secretion, intestinal motility or anatomic integrity is altered, the flora of the small bowel may be affected. Under these conditions large numbers of facultative aerobes (e.g., *Escherichia coli)* and obligate anaerobes *(Bacteroides fragilis* and other fecal anaerobes) may be found in this area. A malfunctioning ileocecal valve could permit these aerobic and anaerobic bacteria to colonize the ileum.

Problems in diagnosis: Even though the methods currently used for culturing anaerobes have been greatly improved, bacterial cultures from intra-abdominal sites can be diagnostically misleading. Anaerobes are the most often overlooked category of potentially pathogenic organisms because their detection demands meticulous collection and culture techniques. The cultivation of certain anaerobes may require up to ten days of incubation, and even a brief exposure to air can kill many of them. Multiple pathogens are frequently encountered, and one organism can overgrow another on the culture plate. Blood cultures can be similarly deceptive, since all significant pathogens in a mixed infection are rarely isolated in a single culture.

Sometimes only the consistent reappearance of a given microorganism in repeated cultures is the clue to clinical importance.

Please turn page for information on one antibiotic of significance in the treatment of serious anaerobic intra-abdominal infections.

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Therapeutic considerations...

Anaerobic activity: Cleocin® PO_4 (clindamycin phosphate injection) has proved to be effective in a variety of serious intra-abdominal infections caused by susceptible anaerobic organisms including gram-positive cocci, and gram-positive and gram-negative bacilli. Specifically, the activity of clindamycin has been established in the following conditions: septicemia; serious intra-abdominal infections such as peritonitis and intra-abdominal abscess; serious infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal-cuff infection caused by susceptible strains of bacteroides, fusobacteria, eubacteria, actinomyces, peptococci, microaerophilic streptococci, and clostridia.*

Since disc susceptibility testing with current methods is not reliable for anaerobes, *in vitro* dilution methods should be used to determine susceptibility to clindamycin.

Effective in serious aerobic gram-positive infections caused by susceptible streptococci, staphylococci, and pneumococci. The use of Cleocin PO_4 in gram-positive infections has been investigated both clinically and bacteriologically. Since it is a parenteral antibiotic, Cleocin PO_4 has been evaluated in serious infections. Its use in these infections should be reserved for penicillin-allergic patients for whom, in the judgment of the physician, a penicillin is inappropriate.

Indications include: serious lower respiratory-tract infections such as pneumonia caused by susceptible staphylococci; serious soft-tissue infections such as deep abscesses and deep traumatic or surgical wound infections caused by susceptible staphylococci and streptococci; septicemia caused by susceptible staphylococci and streptococci; and acute hematogenous osteomyelitis caused by susceptible staphylococci. In many instances the evaluated cases have been secondary to massive wounds, surgery, or debilitating disease. With few exceptions, the organisms proved susceptible *in vitro* and were successfully eradicated from the clinical lesions.

Other therapeutic considerations:

1. Cleocin PO_4 is clinically effective in serious infections caused by penicillin-resistant or penicillinase-producing staphylococci. However, staphylococcal strains resistant to clindamycin have been encountered, and susceptibility testing should be performed.

2. Cleocin PO_4 is useful in patients who are sensitive to penicillin. Clindamycin does not share antigenicity with the penicillins; however, hypersensitivity reactions have been reported with clindamycin therapy. If a hypersensitivity reaction occurs, the drug should be discontinued. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Thus, Cleocin PO_4 can fill a need for both penicillin-sensitive patients and those with serious infections caused by penicillin-resistant staphylococci.

As with all antibiotics, Cleocin PO_4 should be used with caution in atopic patients. Clindamycin has demonstrated cross-antigenicity with lincomycin.

Cleocin PO_4 should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section of the brief summary on the following page.

If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued. (See WARNING box and summary of prescribing information on following page.)

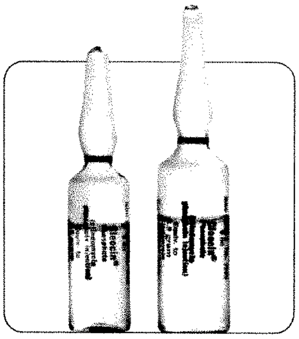
---

*Clostridia are more resistant than most anaerobes to clindamycin. Some species, e.g. *C. sporogenes* and *C. tertium*, are frequently resistant to clindamycin.

STERILE SOLUTION

...Cleocin® PO4

clindamycin phosphate injection, Upjohn



WARNING

Clindamycin can cause severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with the close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin base
benzyl alcohol	5 mg
disodium edetate	0.5 mg
water for injection	qs

When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (e.g., erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings:(See WARNING box.) Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeast. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made.

Local Reactions: Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription.

For additional product information see your Upjohn representative.

MED B-4-S (NFM-3) J-4916-9

STERILE SOLUTION

Cleocin PO4

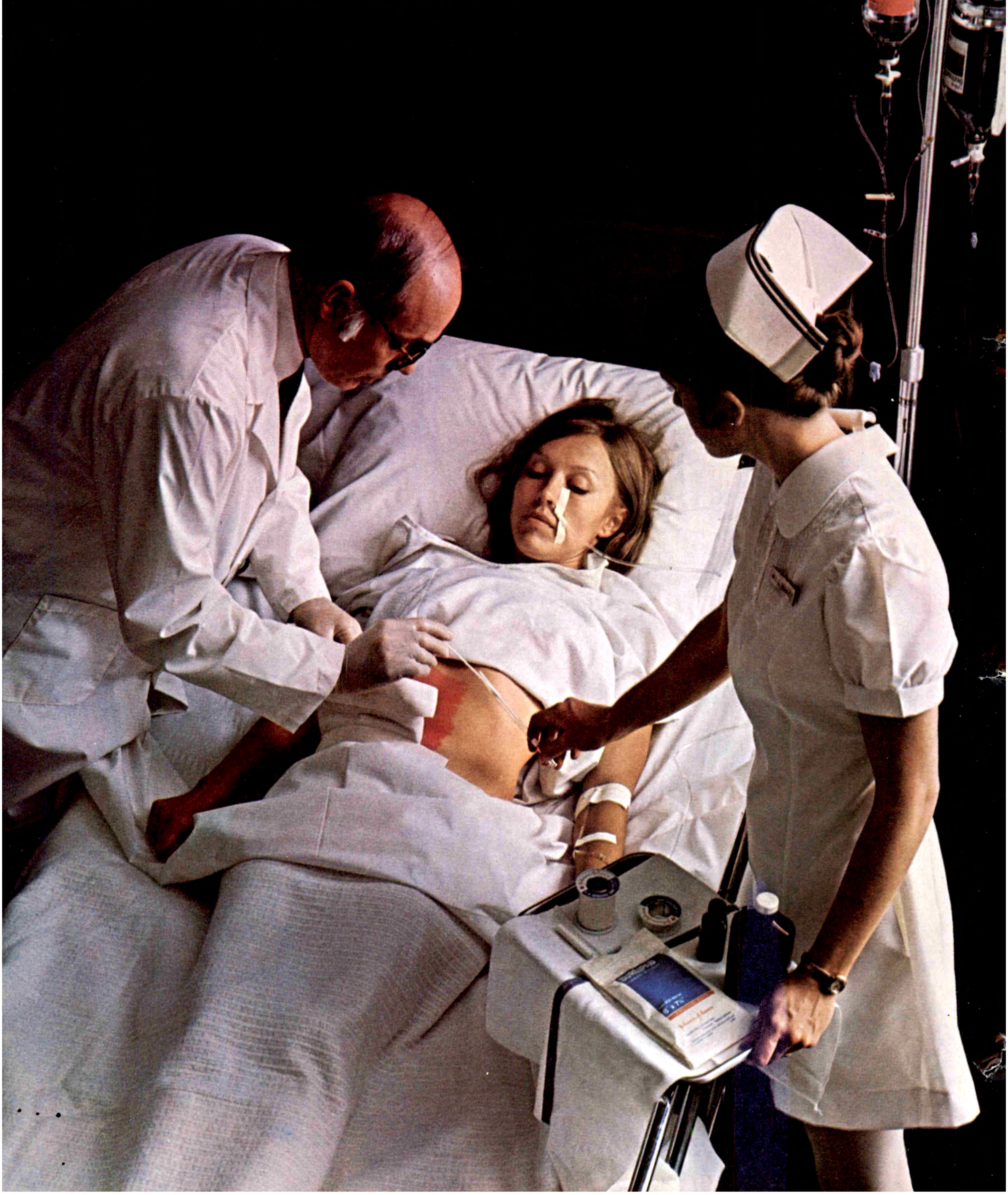
clindamycin phosphate injection, Upjohn

FOR INTRAVENOUS AND INTRAMUSCULAR USE

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001

In serious post-surgical infections*...

*due to indicated susceptible organisms



Until the lab tests come back, start with 'ANCEF'

Serious post-surgical infections usually require immediate treatment. In these cases prudent medical judgment and the use of 'Ancef', when appropriate, can save valuable time while waiting for lab results. 'Ancef' offers:

- **Broad coverage of the major areas of post-surgical infection**

  Skin and Soft-Tissue Infections:
  Staphylococcus aureus (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

  Respiratory Tract Infections:
  Streptococcus pneumoniae (formerly *D. pneumoniae*), *Klebsiella* species, *Hemophilus influenzae*, *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

  Urinary Tract Infections:
  E. coli, *Proteus mirabilis*, *Klebsiella* species and some strains of enterobacter and enterococci.

- **High and prolonged serum levels**
  Single 1 gram IV injections in healthy adult volunteers produced average peak serum levels of 190.0 mcg/ml. At four hours, levels of 16.5 mcg/ml were still present.

- **Convenient IV or IM administration at same dosage schedule**

When lab tests return, if the indicated organism is sensitive to 'Ancef'—and chances are it will be—therapy is already under way. If it isn't sensitive, then 'Ancef' should be discontinued and an appropriate antibiotic should be selected.

Adverse Reactions
Reported adverse reactions include pain on injection, rash, G.I. symptoms, pruritus and phlebitis. For a complete list of reported adverse reactions, please see next page.

Warning: In penicillin-sensitive patients, cephalosporins should be used with caution because of evidence of partial cross-allergenicity of the penicillins and cephalosporins.

Please see next page for a brief summary of prescribing information.

SK&F Smith Kline & French Laboratories
Division of SmithKline Corporation, Philadelphia, Pa.

ANCEF® IV IM
brand of sterile
CEFAZOLIN SODIUM
(LYOPHILIZED)
Injection: 250 mg, 500 mg, and 1 gram vials

ANCEF® IV IM

brand of sterile

CEFAZOLIN SODIUM

(LYOPHILIZED)

Injection: 250 mg, 500 mg, and 1 gram vials

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

DESCRIPTION

Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro*:

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Streptococcus pneumoniae (formerly *D. pneumoniae*)
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole positive Proteus (*P. vulgaris, P. morgani, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Klebsiella* species, *Hemophilus influenzae*, *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx, however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus*.

Septicemia due to *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli*, and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE CEFAZOLIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to 'Ancef'.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported.

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for pneumococcal pneumonia is 500 mg. every 12 hours. In acute, uncomplicated urinary tract infections, usual dosage is 1 gram every 12 hours. In mild infections caused by susceptible Gram positive cocci, usual dosage is 250 to 500 mg. every 8 hours. In moderate to severe infections, usual dosage is 500 mg. to 1 gram every 6 to 8 hours. 'Ancef' has been administered in dosages of 6 grams per day in serious infections such as endocarditis.

'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 ml./min. or greater or a serum creatinine of 1.5 mg. % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 ml./min. or serum creatinine of 1.6 to 3.0 mg. % can also be given full doses, but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11 to 34 ml./min. or serum creatinine of 3.1 to 4.5 mg. % should be given 1/2 the usual dose every 12 hours. Patients with creatinine clearance rates of 10 ml./min. or less or serum creatinine of 4.6 mg. % or greater should be given 1/2 the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

HOW SUPPLIED

Ancef (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg. or 1 gram of cefazolin; in Overfill ("piggyback") Vials for intravenous admixture equivalent to 1 gram of cefazolin; and in Pharmacy Bulk Vials equivalent to 5 grams or 10 grams of cefazolin.

Smith Kline & French Laboratories
Division of SmithKline Corporation, Philadelphia, Pa.
SK&F

Unified Approach to Carcinoma of the Esophagus

WARD O. GRIFFEN, JR., M.D., Ph.D., MICHAEL E. DAUGHERTY, M.D.,
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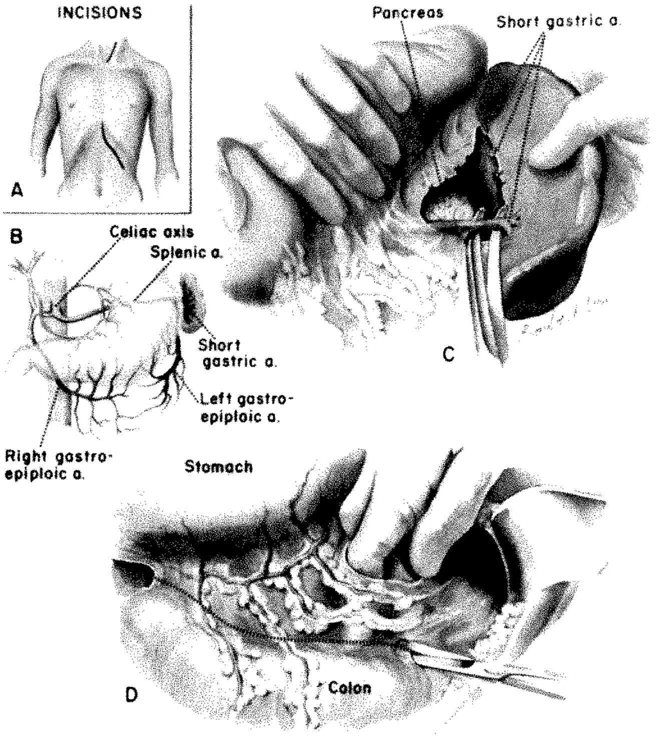
The reversed gastric tube is advocated as a technique to be used in all patients who have carcinoma of the esophagus, whether the lesion is located in the upper, middle or lower esophagus. The tube, constructed out of the greater curvature of the stomach and supplied by the gastroepiploic vessels, invariably has adequate length and sufficient blood supply to heal per primum or to close anastomotic leaks spontaneously when they occur. Since the procedure requires a celiotomy and an incision in the neck, the presence and extent of metastatic disease below the diaphragm and above the clavicle can be evaluated. With prompt resumption of eating, the patients' nutritional status rapidly improves so that they can maintain weight during postoperative irradiation or further surgical procedures, e.g. esophagectomy. It is also effective as a palliative procedure since the patients handle their saliva and other secretions adequately after the procedure.

THE RESULTS of the surgical management of carcinoma of the esophagus are discouraging. Because of this some physicians assume a nihilistic attitude in the management of this disease. Even the most optimistic surgeon who undertakes the care of patients with esophageal carcinoma realizes that most of his efforts will be to produce significant palliation while curing an occasional patient. Failure to cure a patient with carcinoma of the esophagus is usually because of relatively local recurrence of the disease rather than widespread metastases.

In analyzing the reason for failures following surgical extirpation of the esophageal carcinoma, several factors can be cited. First, delay in making the diagnosis often means that a patient already has lymph node metastases when therapy is undertaken. Secondly, the high mortality and morbidity associated with surgical procedures on the esophagus leads to premature death or abandonment of the therapy. A third factor is that although the bulk of the tumor may be in the upper middle or lower third of the esophagus, tumor cells can be found throughout the length of the esophagus.[2]

In this paper we report the concept of using a reversed gastric tube (RGT) made from the greater curvature of the stomach and based on a vascular supply from the gastroepiploic vessels in *all* patients with carcinoma of the esophagus. After the diagnosis has been established by biopsy and the patient prepared for the surgical procedure, construction of the reversed gastric tube allows one to assess intra-abdominal structures as well as the lymph nodes above the clavicle and the cervical esophagus for evidence of metastatic disease. The esophagogastrostomy in the neck either heals per primum, or should a fistula develop, it usually closes promptly allowing the patient to resume normal oral alimentation early after the RGT procedure. If metastatic disease is found, palliative irradiation can be given to the thoracic esophagus in order to retard growth of the tumor. If no metastatic disease is found, several options are available: 1) immediate esophagectomy through a right thoracotomy; 2) irradiation to the lesion at a tumor-killing dose; or 3) preoperative irradiation followed by esophagectomy. Since the RGT procedure can be used in patients who have high, middle or low lesions of the esophagus as well as in patients with or without metastatic disease, this approach can be called a unified management scheme for all patients with carcinoma of the esophagus.

Presented at the Annual Meeting of the Southern Surgical Association, December 8–10, 1975, The Homestead, Hot Springs, Virginia.



FIGS. 1[a to d]. a) Abdominal and cervical incision. b) Discontinuous right and left gastroepiplioic vessels. c) Spleen removed taking vessels close to spleen. d) Omentum taken off at avascular attachment to the colon.

Operative Technique

The fundamental steps of the operative procedure have been described in previous publications.[4,5] A midline or extended left subcostal incision is used and thorough intra-abdominal search for metastases is conducted. Care is taken to divide the gastrocolic ligament adjacent to the transverse colon. This step ensures preservation of the gastroepiploic vessels even when the gastroepiploic arcade is discontinuous, as often occurs. The spleen and tail of the pancreas are mobilized medially, and splenectomy is performed, ligating all vessels close to the splenic hilum (Figs. 1a to d).

Construction of the reversed gastric tube is then carried out using the GIA surgical stapling device, beginning approximately 5 cm proximal to the pylorus, proceeding as far proximally on the greater curvature as necessary to obtain adequate length of the tube. A continuous seromuscular stitch is used to reinforce the staple line of the tube and the gastric closure (Figs. 1, e to g). At this point some of the peripheral portion of the greater omentum can be carefully excised, ascertaining right gastroepiploic pulsations before transection of each occluded segment. All remaining greater omentum is wrapped around the tube.

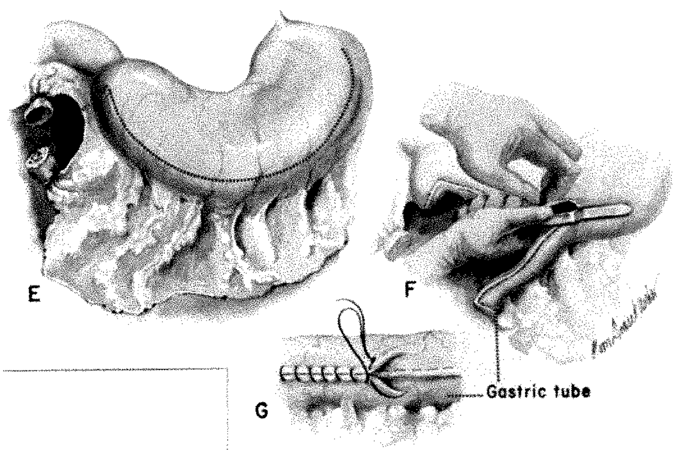
Subsequently, or simultaneously if another operating team is employed, the cervical esophagus is exposed through an incision along the anterior border of the sternocleidomastoid muscle. Lymph nodes suggestive of metastatic disease may be sent for microscopic examination. The esophagus is delivered into the wound, stapled and transected so that a segment of the esophagus may be sent for histologic examination. The stapled distal end of the esophagus may be oversewn with sutures and then is allowed to retract into the mediastinum (Figure 1, h to j). An ample substernal tunnel is created by manual blunt dissection. If no metastases are present and future esophagectomy is anticipated, the gastroesophageal junction is stapled and transected, and pyloroplasty is carried out.

Completion of the esophageal replacement is accomplished by passage of the reversed gastric tube through the substernal tunnel to the neck, where a two layer end-to-end anastomosis to the proximal cervical esophagus is carried out (Fig. 1k). Operating time is shortened by simultaneous abdominal closure and gastrostomy, if elected, during the performance of the cervical anastomosis and closure of the neck incision (Fig. 1l).

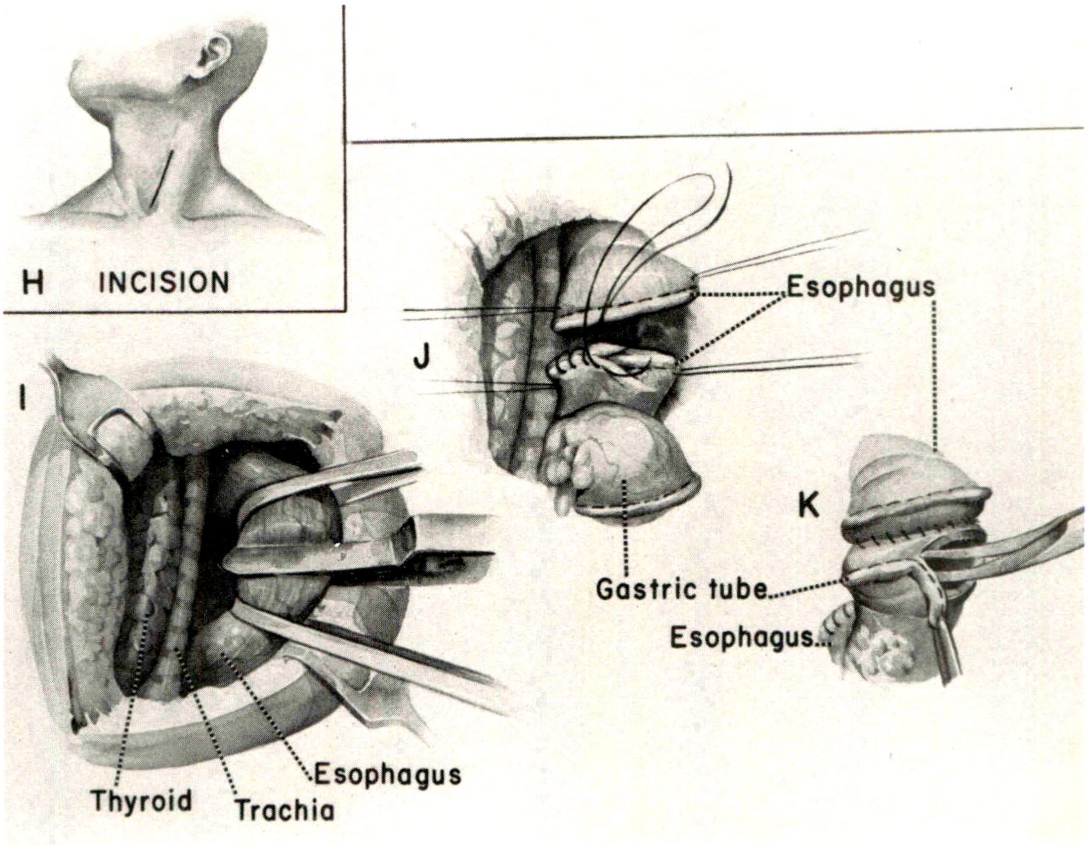
Gastric decompression is maintained for 5 days and the patient is encouraged to expectorate all saliva. If a barium swallow obtained 7 days postoperatively demonstrates satisfactory continuity, the patient begins taking liquid feedings, progressing to a regular diet over the next several days. The presence of a small fistula mandates a liquid diet until spontaneous closure, while larger leaks necessitate parenteral or tube alimentation.

Clinical Material

Ten patients with squamous cell carcinoma of the esophagus underwent esophageal replacement with a reversed gastric tube (Table 1). Mean age of the patients



FIGS. 1[e to g]. e) Outline of proposed gastric tube. f) GIA stapler in place to transect a portion of the stomach. g) Running 3–0 silk closure of staple line.



FIGS. 1[h to k]. h) Cervical incision along anterior border of sternocleidomastoid muscle. i) Esophagus delivered through wound ready for transection. j) Esophagus transected and distal staple row being oversewn (after biopsy). k) Anastomosis between gastric tube and proximal esophagus.

was 56 years, with 4 patients under 50 years of age. Seven of the 10 patients were limited to liquid intake at the time of their presentation. Average weight loss for all patients was 10 kg. Seven lesions were in the middle third and 3 lesions were in the distal third of the esophagus. Five patients had intra-abdominal metastases, and no cervical metastases were found.

Comment

By the late 19th century many surgeons were contemplating resection of lesions of the esophagus. Such thoughts led to the consideration of establishing continuity between the esophagus and the stomach. By the time the first successful resection of the human thoracic esophagus for carcinoma had been performed in 1913,[13] all of the useable autologous organs had been described as replacements. In 1904 Wilstein first used the jejunum for antethoracic esophagoplasty[15] and in 1907 Roux reported the first successful use of jejunum as an esophageal replacement.[11] In 1905 Beck described the use of a tube of stomach formed from the greater curvature, to replace the esophagus in dogs.[1] In 1912 Jianu[6] independently described the same technique and in that same year Ropke[10] first successfully used it in man. Finally, in 1911, Kelling discovering that he was unable to use the jejunum for esophageal replacement due to a short mesentery, employed the transverse colon for an antethoracic esophagoplasty.[7] In addition, the technique of segmental resection of a lower esophageal lesion and reconstruction by an esophagogastrostomy had been described in 1908.[14] By 1923 Ochsner and Owens,[9] writing about

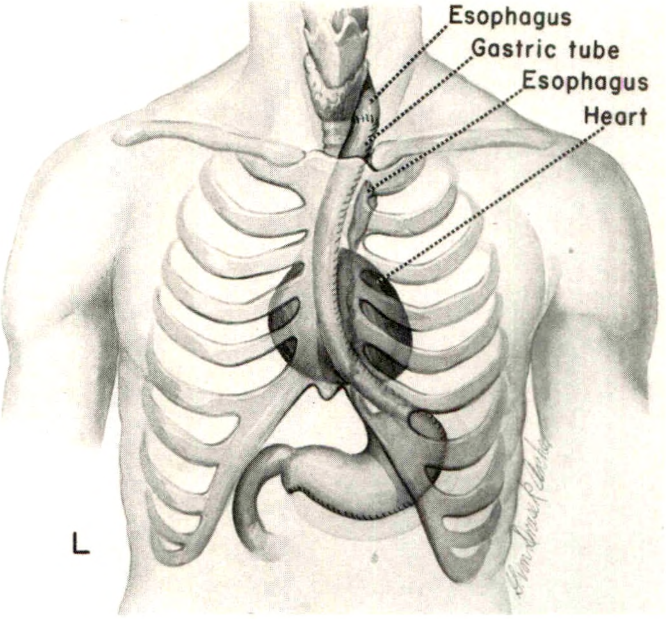


FIG. 1[l]. Completed reversed gastric tube procedure.

benign strictures of the esophagus, were able to compile a sizable number of cases using stomach, jejunum, or colon as esophageal substitutes. The ensuing years have seen refinement of these techniques. Controversies have developed over the superiority of right thoracotomy or left thoracoabdominal incision, the right or left colon as a substitute, and the subcutaneous, retrosternal or intrathoracic positioning of the esophageal substitute. All procedures have had their particular advocates.[8-12]

In 1951 Gavriliu first began using the reversed gastric tube to bypass obstructions of the esophagus.[4] By 1975 he was able to write a monograph describing 526 reversed gastric tube procedures with 21 deaths (3.6%) and an anastomotic leak rate of 7.65%.[3] Most of the procedures were done for benign strictures of the esophagus, but carcinoma of the esophagus is included among his patients and the results seem encouraging.

The results reported in this series of 10 patients seem to indicate a high complication rate, namely 6 cervical anastomotic breakdowns and a significant mortality. As our experience with the RGT procedure increases, including a number of patients with benign esophageal lesions, the complications and mortality are steadily decreasing. The advantages of this procedure seem to be: 1) technical ease; 2) generally excellent blood supply and adequate length, both of which contribute to prompt healing of any fistulas that occur; 3) retrosternal placement of the tube permits early postoperative irradiation to the posteriorly placed esophagus. In addition, the RGT technique allows prompt gross and histologic evaluation of the celiac nodes, liver, and other intra-abdominal organs to which the tumor might metastasize, as well as cervical lymph nodes and the cervical esophagus itself. This enables one to predict prognosis and also to state whether a cure may be obtainable in a given case.

TABLE 1. *Patient Data*

Age, Sex	History	Wt. Loss	Operative Findings	Hospital Course	Follow-up
70, M	Dysphagia, 3 mos; liquids only, 1 mo	13 kg	Celiac metastases	No complications; dismissed 20 days postop	Gained weight Died 3¼ mos
46, M	Dysphagia, 6 mos; liquids only, 6 wks	21 kg	Celiac metastases	Anastomotic fistula, spontaneously closed. Dismissed 27 days postop	Irradiation Maintained weight Died 4 mos
48, M	Dysphagia, 4 mos; liquids only, 1 mo	18 kg	Celiac metastases; Subcutaneous reversed gastric tube	Venous infarction of tube Dead, 6 wks postop of sepsis	Postoperative mortality
66, M	Dysphagia, 5 mos	0 kg	No metastases	Anastomotic fistula, spontaneously closed. Dismissed 21 days postop	Maintained weight Esophagectomy 6 wks Died, 3 mos, cardiac disease
57, M	Dysphagia, 2 mos; liquids only, 3 wks	14 kg	Lesser curvature metastases	Anastomotic fistula, spontaneously closed. Dismissed 16 days postop	Irradiation Gained weight Died 6½ mos
54, F	Dysphagia, 6 mos; liquids only, 1 mo	14 kg	No metastases	Anastomotic fistula, prolonged closure. Severe depression Anastomotic dilation Dismissed 3 mos postop	Maintained weight Died, 5 mos
71, M	Dysphagia, 1 mo	11 kg	No metastases	Anastomotic fistula Died, 1 mo, sepsis & metabolic complication	Postoperative mortality
47, M	Alcoholic Dysphagia, 6 wks	0 kg	No metastases	No complications Dismissed 17 days postop	Irradiation Maintained weight Esophagectomy; died 5 mos, mediastinal abscess
45, F	Stricture, 34 yrs Dysphagia, 2 mos; liquids only, 2 mos	7 kg	No metastases	Anastomotic fistula, spontaneously closed. Dilation required. Dismissed 21 days postop	Gained weight Esophagectomy 3 mos Alive, 5 mos
58, F	Irradiation 8 mos previously Dysphagia, 6 mos; liquids only, 1 mo	0 kg	Celiac metastases	No complications. Dismissed 14 days postop	Maintained weight Alive, 4 mos

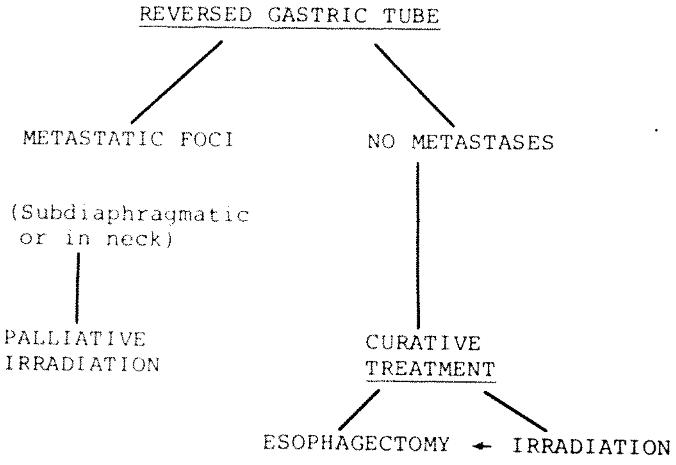


FIG. 2. Management scheme for all patients with carcinoma of the esophagus.

The palliative features of a reversed gastric tube should also be emphasized. As demonstrated in these 10 patients, regular oral alimentation resumes rather promptly even when a fistula occurs. The ability to handle saliva and other secretions continues until the demise of the patient. During postoperative irradiation the patients are able to maintain their weight because of adequate oral intake. Finally, prompt relief of the esophageal obstruction diminishes pulmonary complications.

Thus, the reversed gastric tube procedure, although not new, seems to fit the criteria for providing a unified approach to all patients with carcinoma of the esophagus. It relieves the esophageal obstruction promptly. It allows adequate assessment of the areas to which tumor is likely to spread so that a decision can be made regarding long-term results. Finally, it seems to be a procedure which with increasing experience will carry a low mortality and only a moderate morbidity, much of which is corrected promptly so that the patient can resume relatively normal eating habits. As depicted in Fig. 2, the scheme of management of all patients with carcinoma of the esophagus could be a reversed gastric tube followed by either palliative postoperative irradiation to the esophageal lesion if metastases are found or tumoricidal irradiation, esophagectomy, or combination irradiation and surgical extirpation as a curative procedure in a patient who will be able to maintain nutrition because of a well-functioning reversed gastric tube.

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DISCUSSION

DR. EDWARD F. PARKER (Charleston, South Carolina): I'd like to present a contrasting point of view. We believe that the use of irradiation first might obviate the need for bypass, since it is possible that the ability to swallow might be restored by the x-ray therapy. (Slide) This is illustrated by these photographs before and after x-ray therapy which show relief of obstruction radiographically, and there was concomitant restoration of the ability to swallow. One might ask, if such a patient had already had a reversed gastric tube, what would be accomplished by palliative radiation therapy, if it had already been decided that the disease was incurable because of metastases found at the time of laparotomy or collotomy, or both, and if the ability to swallow had already been restored.

We would consider the bypass operation initially a very major one, because very many of our patients look like this on admission. Such patients with varying degrees of malnutrition, in our hands, unfortunately, simply have not tolerated an operation of that magnitude without excessive morbidity and mortality.

If we use x-ray therapy first, and it's not followed promptly by improvement in swallowing and nutrition, we prefer to defer major operation until the patient's metabolic state is no longer catabolic. This is done by completing the x-ray therapy, usually 4500 rads in three weeks, and by concurrent transnasal intragastric tube feeding—there aren't many that can't be passed—or at times by intravenous hyperalimentation. As a last resort, we would use gastrostomy, the presence of which does not interfere with subsequent use of the stomach as a whole organ transplant, or with the use of a tube therefrom.

One exception is in the patient with the usually sudden development of esophagobronchial fistula, in whom we perform the same bypass operation promptly, using, usually, the left colon, although I agree that the gastric tube may be or should be used more, in order to prevent suppurative bronchopulmonary disease, which is, again, pretty grim.

After we complete the x-ray therapy, if the patient is otherwise operable, we advise operation and resection in one stage, when he or she is in good condition.

(Slide) We just have had much better success in operating upon people whose esophagus looks like this, which is a gross specimen which looks almost normal, after removal, after treatment by x-ray, than we have in the earlier stages.

We advise the operation, even though the patient has an excellent result, because on microscopic examination there is residual carcinoma in a high percentage of these; about 86%. Therefore, by using the principle of x-ray therapy first, in all in whom it is tolerable, and concurrent intensive therapy for malnutrition, and, thereafter, resection in all those who are operable and theoretically resectable, our long-term results have been as follows: In the last 138 cases, whom it was possible to follow at least five years, by x-ray therapy alone the results have not been as good as with x-ray therapy followed by resection, in suitable cases. And in the entire series one can see that the results have been 12% for two-year survival, and 8% for five-year survival.

We commend again Dr. Griffen and his associates for this work, and we certainly intend to use the reverse gastric tube more, instead of the whole stomach or the colon, in the future. We have given up the jejunum long ago, because we had even less success with that.

DR. RAYMOND W. POSTLETHWAIT (Durham, North Carolina): We have been trying to find a satisfactory means of palliation for those patients with invasion of the trachea and bronchi or actual fistula formation. Colon interposition, in our experience, resulted in an unacceptable morbidity and mortality, even in these high risk patients.

In the past year we have utilized a Beck tube for ten patients, with one postoperative death. This was not due to the tube or any complications of it. The tube is formed from the greater curvature of the stomach, but is isoperistaltic, the blood supply being from the right gastroepiploic vessels. The spleen is not removed, and no dissection about the pancreas is required, as described by Heimlich.

Brought substernally, it reaches easily into the neck. Because of leaks at the cervical anastomosis, in our last three patients we have brought out the tip of the tube on the skin of the neck as a controlled fistula, to be closed about the eighth day. The esophagus is anastomosed end to side into the tube opposite the tube suture line.

Although long-term survival cannot be anticipated, these patients can have an adequate intake without the discomfort and the complications of constant aspiration.

DR. MICHAEL E. DAUGHERTY (Closing discussion): My congratulations go to Dr. Parker's radiation therapists, who were able to treat patients such as he showed with radiation preoperatively, in order to diminish the obstruction of the lesion. Our radiation therapists have not been as effective, and our patients have not been able to tolerate irradiation when they present with obstructing lesions, and their obstruction has not been relieved, for the most part.

Several radiologists around the country have reported that in patients who present with annular constricting lesions and esophageal obstruction, radiation therapy often is not able to relieve the obstruction.

I thank Dr. Postlethwait for his comments. Certainly, the modification of using the gastric tube with the right gastroepiploic vessels is one which works just as well in his hands; and I think his support of the use of the tube to alleviate the pulmonary complications is one of our major reasons for proposing the advantages of the use of the gastric tube for esophageal replacement.

The Treatment of Hemangiomas:

With Special Reference to the Role of Steroid Therapy

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Hemangiomas are the most common of all human birth defects. The author has reviewed a 25-year personal experience with treatment of over 1000 patients with a variety of common and rare developmental vascular anomalies. Attention is given to a more useful clinical classification of these disorders. The classification is intended to be helpful in estimating prognosis of the lesions and as a guide to the choice of therapy. Many treatment modalities are evaluated—some successful and some quite disappointing. Surgical excision, irradiation, CO_2 freezing, sclerosing agents, cauterization, steroid therapy and watchful waiting are among the treatment methods evaluated. High dose—short course Prednisone therapy has proved to be a major new addition to the treatment of massive juvenile capillary hemangiomas. Numerous misconceptions have appeared in the medical literature. These are noted and a philosophic basis for present day management is suggested for each type angioma. The roles of growth, resolution, histologic picture and sense of deformity are considered in viewing the surgeon's approach to these difficult and challenging problems. Some evidence and speculations are offered as to the etiology, neurogenic influences and physiological dynamics of the various hemangiomas.

HEMANGIOMAS are the most common congenital anomalies in humans and they present physicians with some of the most difficult treatment problems known to medicine.

Hemangiomas are *not* true neoplasms despite the fact that they have the potential to grow. They might be defined as congenital hamartomas, representing mesodermal rests of vaso-formative tissue. As they enlarge, neo-vascularization occurs by canalization of solid masses of endothelial cells.

There is much confusion and disagreement in the medical literature concerning the nature and management of hemangiomas. This confusion stems from the fact that the term "hemangioma" has been used loosely in medical literature for many years to include a great variety of very diverse clinical conditions. Classification of angiomas is further complicated by the marked limitations in the ability of the medical pathologist to separate the clinical varieties of hemangiomas on the basis of histologic sections. All hemangiomas have abnormal patterns of hemodynamics, and these *physiological* differences, not seen in fixed sections, are largely responsible for the great clinical variations in different varieties of hemangiomas.

The prognosis of two different types of hemangioma may vary from rapid and complete involution to continous progression leading to ulceration, infection, heart failure and even death. The choice of the optimum method of treatment for a given hemangioma not only depends on the specific variety of hemangioma under consideration, but also may change with its precise extent, the age of the patient and the exact anatomical location of the angioma. Both treatment and prognosis of hemangiomas are further complicated by the fact that the congenitally predetermined ultimate extent and pattern of a given hemangioma may be occult and completely indeterminate at the time of initial diagnosis. A workable classification of hemangiomas should provide guidance as to the most appropriate treatment program to be followed (Table 1).

Over the past 25 years the author has personally dealt with several thousand hemangiomas, including examples of all categories listed in Table 1. A large variety of proposed treatment methods have been tried

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TABLE 1. *Classification of Hemangiomas*

- Type 1: Neonatal Staining
- Type 2: Intradermal Capillary Hemangiomas
  - A. Salmon Patch
  - B. Port Wine Stain
  - C. Spider Angiomas
- Type 3: Juvenile Hemangiomas
  - A. Strawberry Mark
  - B. Strawberry Capillary Hemangioma
  - C. Capillary Cavernous Hemangioma
- Type 4: Arteriovenous Fistulae
  - A. Arterial Hemangiomas
  - B. Hemangiomatous Giantism
- Type 5: Cirsoid Angioma (racemose aneurysm)

when appropriate indications existed. A number of lessons have been learned concerning the benefits and limitations of these treatment methods. This paper will attempt to summarize (and possibly oversimplify) the basic principles of selection and timing of treatment approaches for each of the principle varieties of hemangioma.

Treatment of Hemangiomas Based on Clinical Classification

Type 1: Neonatal Staining

This condition is present at birth and is seen as a light pink staining pattern of the skin usually located in the midline of the base of the neck over the ligamentum nuchae, or over the glabella region of the forehead. It is occasionally seen over the sacrum. This condition almost always fades spontaneously with a few months, and no treatment is indicated.

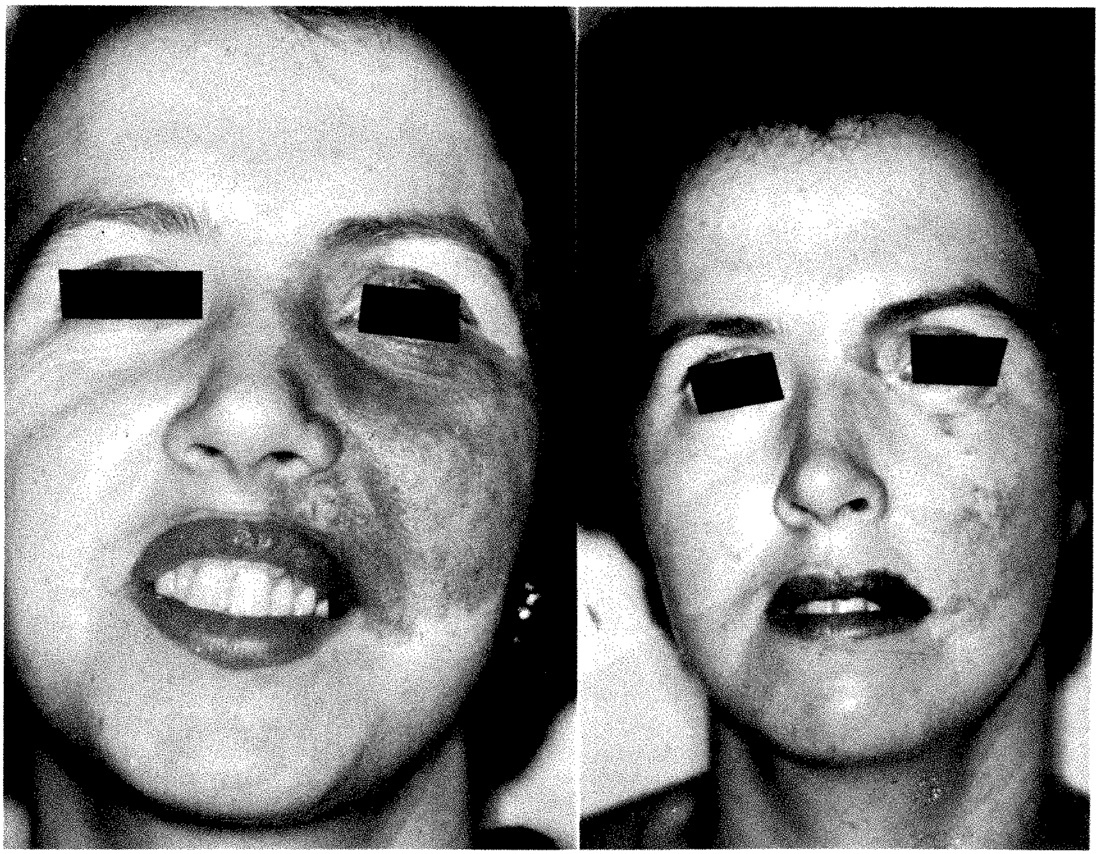
Type 2: Intradermal Capillary Hemangiomas

These are usually present at birth. The endothelium shows adult type morphology and is located in the deep dermis. The discoloration patterns correspond to the skin distribution of various branches of sensory nerves. On the face, they most commonly reflect patterns of the trigeminal nerve branches. There are three varieties:

The salmon patch: This is an extremely faint variety of intradermal hemangioma with a light pink to rust color. It blanches on pressure, is not elevated above the skin surface, and its pattern does not change over a period of years. It is not sensitive to x-ray therapy, surface dessication, freezing, surgical shaving, or abrasion.

Treatment consists of no treatment, use of make-up creams (in females only), or medical tattooing with insoluble pigments. In very exceptional cases, removal of the salmon patch and skin grafting may be indicated when the sense of deformity is marked.

Unfortunately, tattooing requires multiple treatments, often over a period of years, and although the color may



FIGS. 1a and b. (left) Young school teacher with port wine stain involving skin innervated by maxillary division of left trigeminal nerve. She had tried to cosmetically cover the area for several years but found this tedious and stated "it did not make me feel any less disfigured." Radioactive thorium had been tried but proved unsuccesful. (right) One-stage massive skin grafting of the left cheek, left nose, left lower eyelid, and left upper lip was carried out in a single operation. The skin graft was taken from the anterior and lateral aspect of the left neck at a setting of 0.012 of an inch. Only the light port wine stain in the left upper medial eyelid and that within the vermillion of the lip were left. Patient no longer uses make-up of any kind and has found the removal of the birthmark "most gratifying."

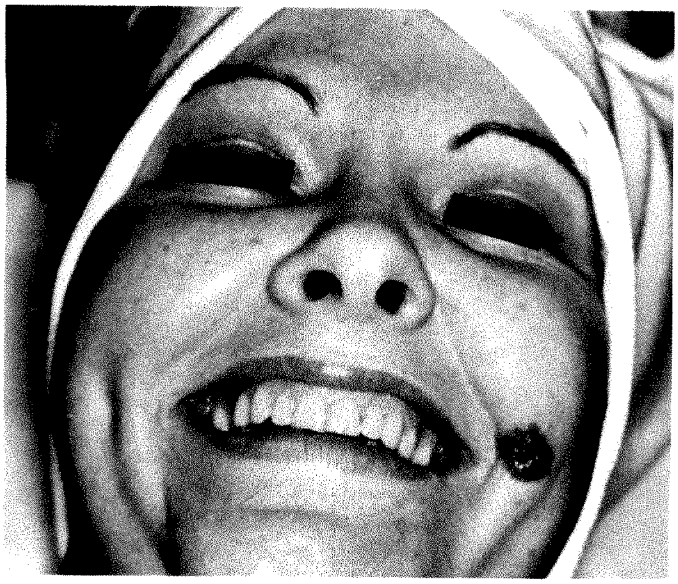


FIG. 2a. This young nurse's mother had been told 20 years earlier that this capillary cavernous hemangioma would "disappear if she would give it time." At 20 years of age, the patient is still waiting.

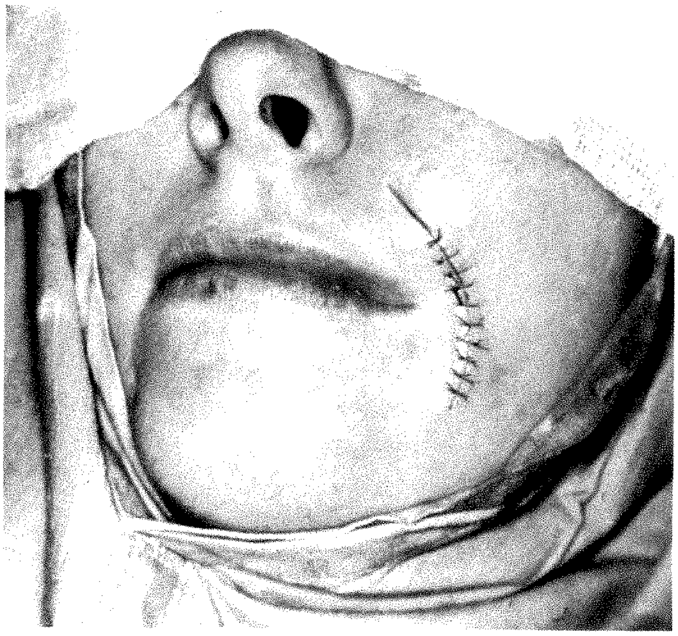


FIG. 2b. This localized hemangioma is removed using a natural skin line of relaxation with plastic closure.

be improved it has not been possible to provide skin tones that will match the changes in the color of the normal surrounding skin. Tattooed angiomas do not show appropriate color variations with changes in temperature and external light reflection. A tan or brownish patch-like effect is often the result.

Port wine stain. The port wine stain is much deeper in color than the salmon patch. It does not enlarge but, with time, often develops hyperkeratotic patches or knobs on its surface. These are similar to changes seen in certain types of pigmented nevi and probably represent abnormalities of cutaneous nerve endings. After many years, the surface of port wine stains may develop a troublesome eczema if untreated.

Treatment: When the port wine stain involves a major area of the face, skin grafting is probably indicated (Figs. 1A and B). Grafts should be patterned to match esthetic facial units to make marginal scarring less conspicuous. Skin grafts should be taken from color-matched donor sites (the scalp or posterior neck) that normally have capillary beds capable of blush responses. This type of grafting must be executed with flawless technique for good results. It is more difficult to obtain perfect results in very young children, but grafting should not be postponed until adult life as *much psychologic damage occurs during the waiting period!* The sense of deformity with a port wine stain is much more consistently present and profound than is generally appreciated.

Spider angiomas. These have a small central dermal arteriole with a network of radiating intradermal capillaries reachiang out in stellate fashion. They are small—but may be multiple—and they often appear at 3 to 4 years

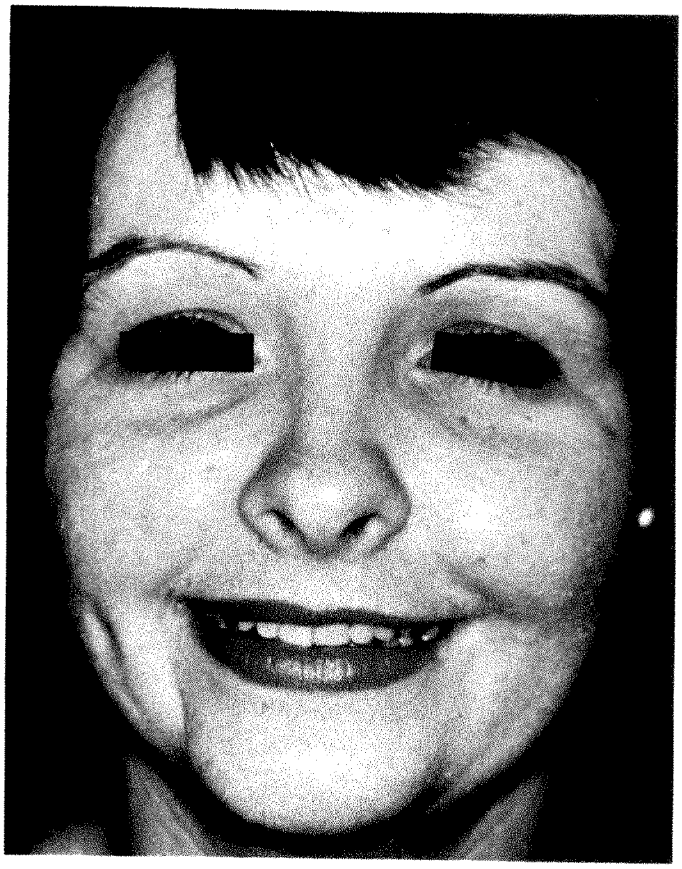


FIG. 2c. This shows the result obtained some months later, the procedure having been carried out under local anesthesia as an outpatient procedure. If the same treatment had been used in childhood, many years of embarrassment would have been avoided.

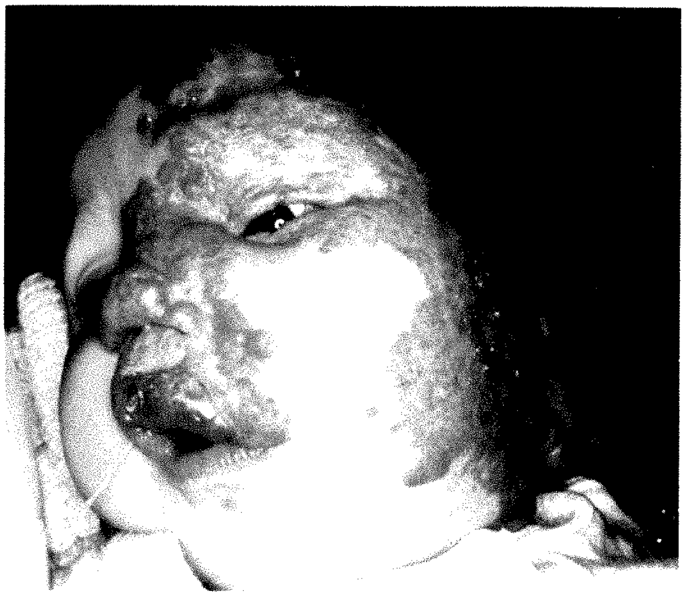


FIG. 3a. This 2-month-old baby has a rapidly enlarging capillary cavernous juvenile hemangioma. The pediatrician seeing this baby urged "watchful waiting."

of age. The pulsations of the central arteriole may be brought out by pressing a glass plate lightly over the spider. They usually require several years for spontaneous resolution.

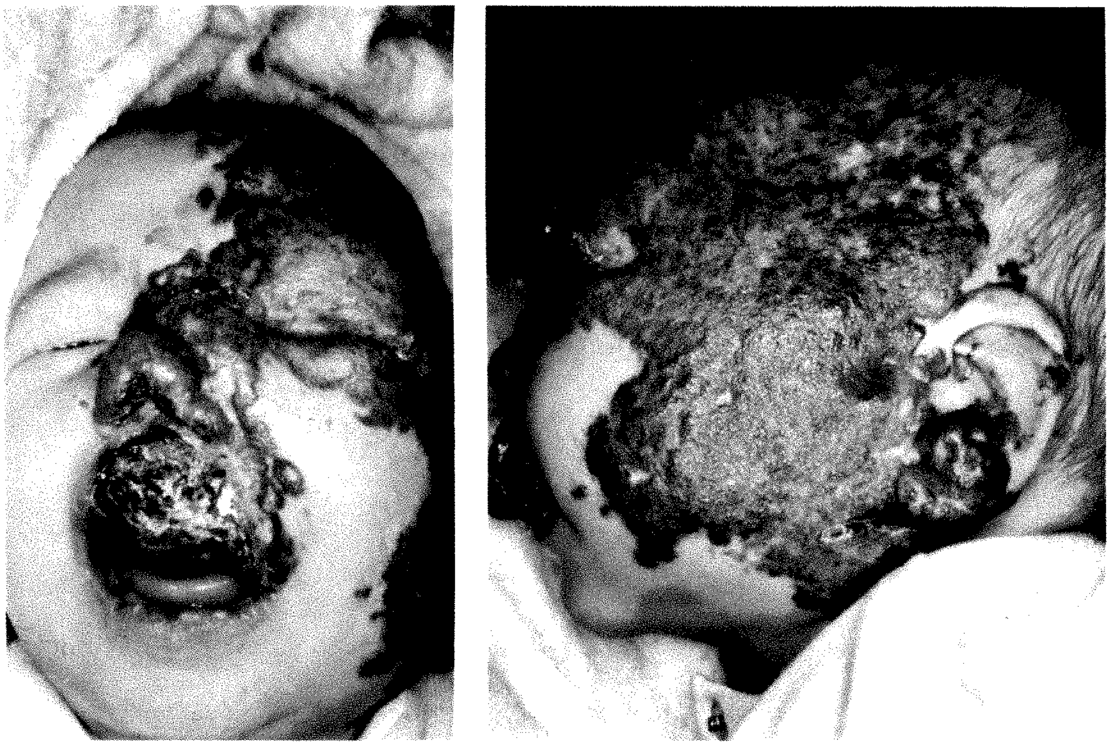
Treatment: If resolution is unduly delayed, they may be treated by fine needle point dessication of just the central arteriole, using magnification.

Type 3: Juvenile Hemangiomas

These are the common lesions described so frequently in the pediatric literature as "always undergoing complete resolution." They represent the only type of hemangioma where resolution plays a significant role in treatment management. There are three varieties:

The strawberry mark. The strawberry mark may be found in approximately one out of every one hundred live births. It consists of a pale halo of skin surrounding a radiating telangiectasis approximately 1–3.5 cm in diameter. The halo may be brought out more clearly by rubbing the skin surface with the finger. Since most of these lesions will disappear spontaneously, they are sometimes thought of as "abortive" angiomas. A few go on to produce a "strawberry mark *en plaque*." Treatment consists of watchful waiting and reassurance.

The strawberry capillary hemangioma. This is perhaps the most common congenital anomaly in children. It may be present at birth but often appears as a tiny red spot in the first days or weeks of life and will grow rapidly in size over the first three months of life. When limited to the surface capillaries of the skin, it may be relatively circumscribed, but is usually moderately elevated above the surface with some degree of lobulation and a bright red color that gives it the name "strawberry." These smaller lesions rarely ulcerate and in the vast majority of instances will undergo spontaneous resolution between about one and 4 years of age. After age 4,



FIGS. 3b and 3c. Within 2 weeks the lesion enlarged to produce ulceration of the upper lip, loss of the columella of the nose, closure of the left eye, blockage of the left ear canal with otitis externa and abscess and drainage from the left parotid gland. The patient developed fever, anemia, and stridor.

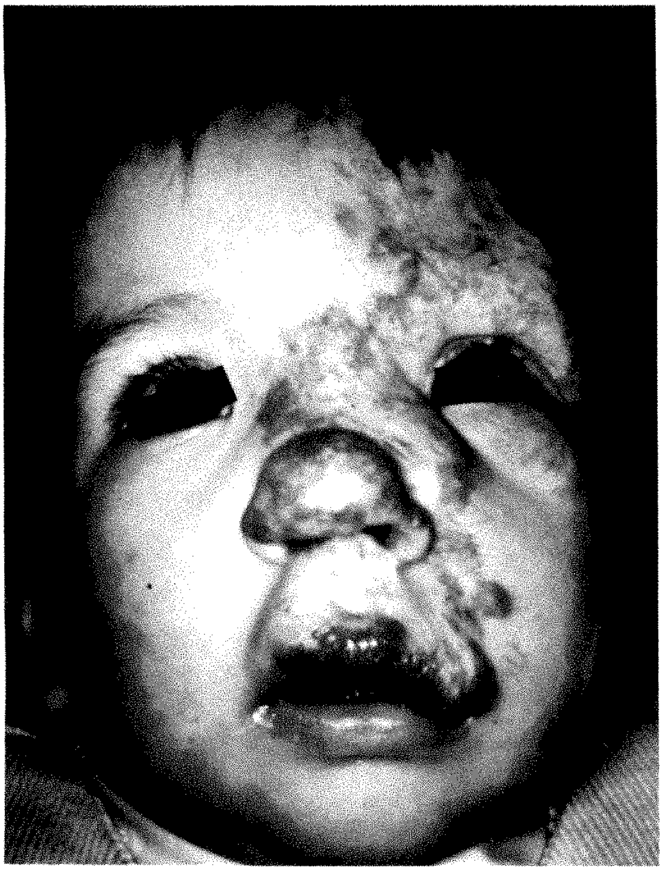


FIG. 3d. Patient was placed on 40 mg of Prednisone q/2 days when seen in the condition of Figs. 3B and 3C. Within 2 weeks there was marked reduction in the size of the lesion and the ulcerations had begun to heal.

spontaneous regression may continue—but only at an extremely slow rate.

Treatment: When these lesions are relatively small and on noncritical areas of the body, spontaneous resolution may give satisfactory results. If ulceration occurs because of irritation or involvement of the surface epithelium, infection and permanent scarring are inevitable. With such lesions early surgical excision may offer the best solution for both child and parents. Even non-ulcerated strawberry hemangiomas may, in many instances, be most effectively managed by simple excision and skin closure (Figs. 2a to c). Modern techniques of plastic skin repair make it possible to greatly minimize surgical scarring and avoid years of deformity and concern about these lesions. To await complete resolution is a disservice to both child and parents in the case of lesions well suited for surgical excision. Irradiation therapy or freezing techniques that will produce ulceration and scarring are contraindicated. Sclerosing agents such as 5% sodium morrhuate (a mixture of the sodium salts in the saturated and unsaturated fatty acids of cod liver oil) should be limited to injections of lesions on the scalp, tongue, buccal surface and other areas where residual scarring is of little concern and surgery may be unnecessary. In these special areas a mechanical device may be used to arrest circulation in the injected area for about 5 minutes to greatly improve the response and sclerosis.

Capillary cavernous hemangiomas: At times juvenile capillary hemangiomas involve not only the cutaneous vessels but also larger venous sinusoids in the deep dermis and subcutaneous tissues. Such hemangiomas may take on gigantic proportions involving major portions of an extremity or several features of a child's face and neck. The growth pattern (most rapid in first 6 months of life) is very similar to that of its smaller cousin, the strawberry capillary hemangioma; but because of its large size and rapid spread, the lesion may progressively involve normal and vital structures with alarming rapidity. Over a period of a few weeks, eyelids, lip vermillion, ear canals, nasal cartilages, and other facial features may be seen to disappear into the elevated and spreading bright red margins of this tumor. Maceration, ulceration, infection, bleeding, scarring, and functional problems related to breathing, vision, hearing and eating may rapidly ensue. If the infection is controlled by antibiotics and the anemia is corrected, spontaneous resolution will occur in such patients, but it is *never complete* and usually is delayed in age of onset in comparison with the smaller more circumscribed juvenile strawberry angiomas. When parents are advised to have no treatment for this lesion and to wait for resolution, they may be dismayed as the days pass while they see enlarging ulcerations with serious scarring, sepsis, fever, anemia and other com-

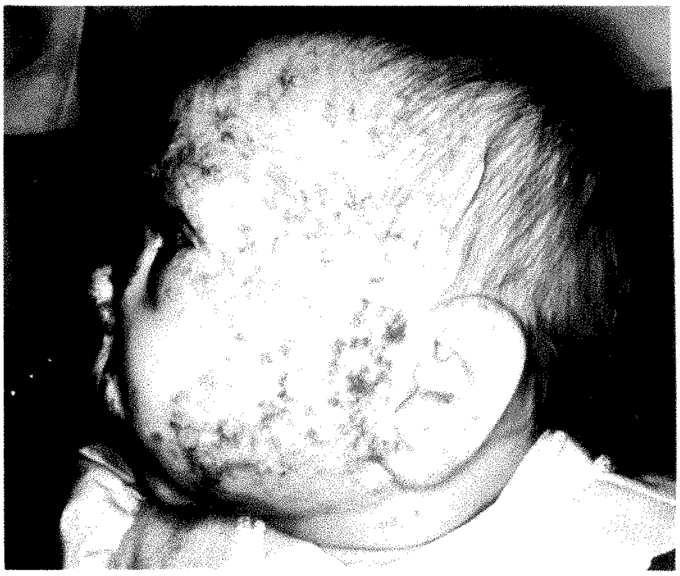
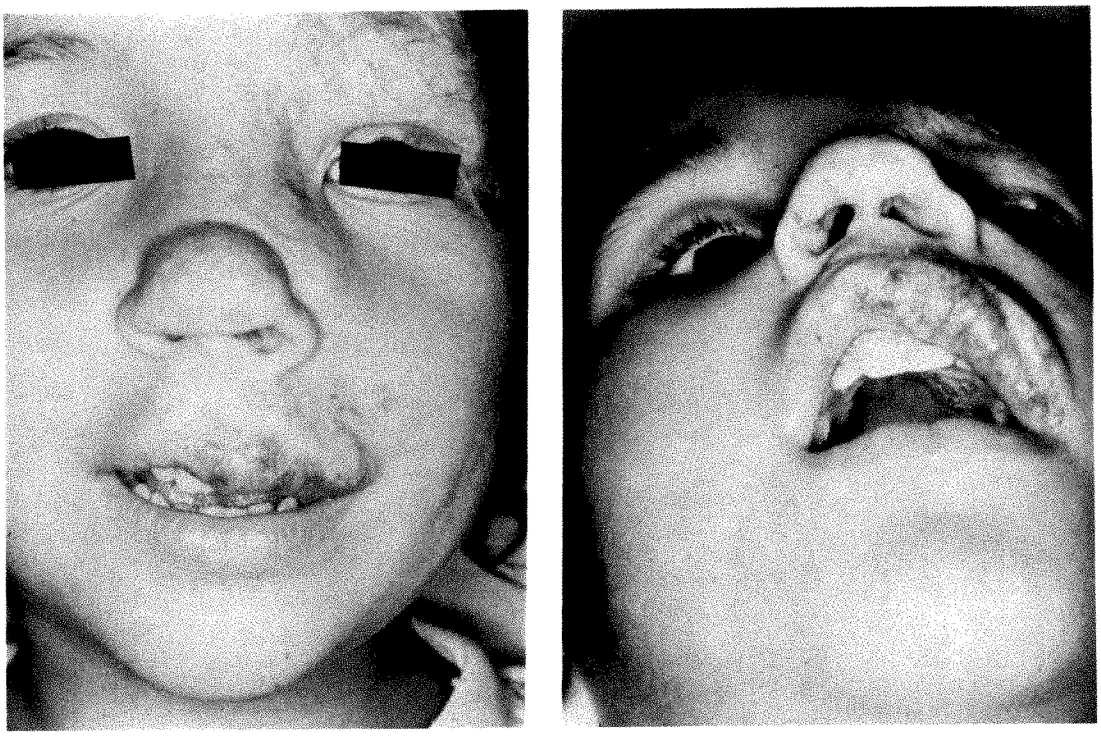


FIG. 3e. Within 5 weeks the condition had markedly improved. The eyes are opened, the ulcerations healed and the deep mass is subsiding in volume. The ear canal is opened and vasospasm and sclerosis may be seen on the left half of the face.



FIGS. 3f and g. At age 5 further resolution of this hemangiom (shown in Figs. 3a through c) had come to a halt for over one year. She was left with residual deep angioma in the upper lip, nasal tip, and left upper eyelid, and with considerable scarring as well as loss of the columella of the nose. Reconstructive surgery was indicated.

plications (Figs. 3a to 3d). Years later children who have been managed by such conservative routines are left with massive deformity. It may be equally unwise and deforming to undertake major surgical resection of these hemangiomas *during the phase of rapid enlargement!* Better treatment of these lesions is now possible.

Role of Steroids in Treatment of Capillary-cavernous Hemangiomas

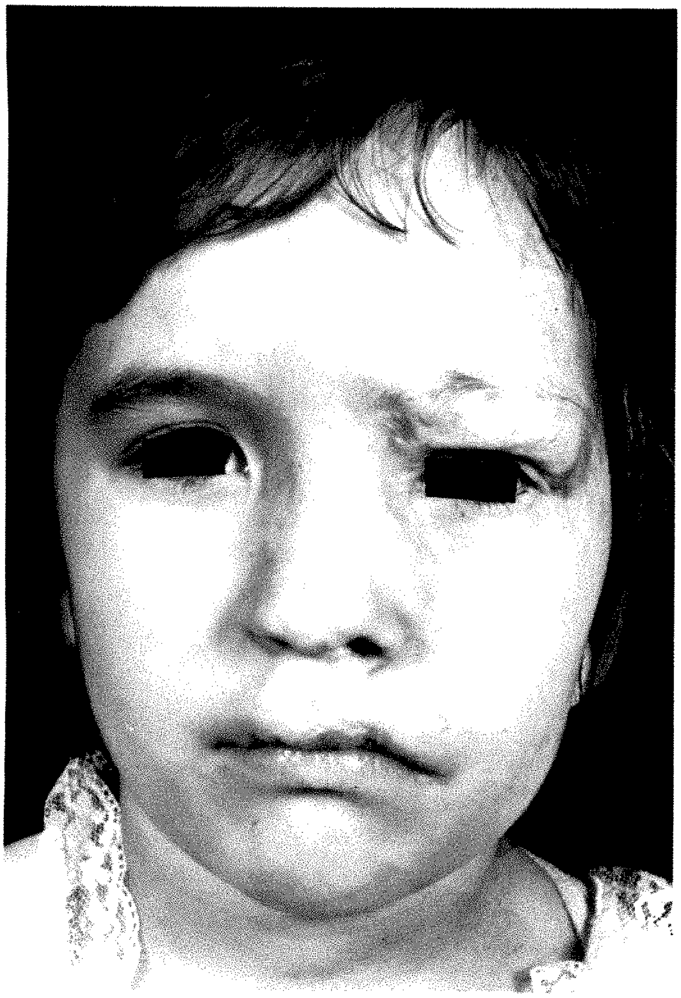
Treatment of the rapidly growing capillary cavernous hemangiomas requires the initiation of a course of steroids (Prednisone) at the earliest possible age. In 1967 we reported the first 7 children who showed uniform and dramatic responses of their massive capillary cavernous hemangiomas to "short course—heavy dose" steroid therapy.[23] Earlier attempts had been made to manage the thrombocytopenia of infants with Kassabach-Merritt Syndrome by the use of steroids, but results had been somewhat disappointing. In a few of those children, the size of the hemangioma had decreased, but platelet levels had not been corrected. Subsequently, Fost and Esterly[6] and Brown, *et al.*[3] have reported confirmation of the gratifying results seen[23] in infants with massive juvenile capillary hemangiomas following treatment with Prednisone.

Since 1967 the author (M.T.E.) has continued to use steroids with this group of patients with a better than 90% dramatic response of these lesions as manifested by marked regression within two to three weeks after starting therapy. With daily (or 1. 2 day) doses of 20–40 mg of Prednisone, one may expect the enlarging hemangioma to stop growing in 3 to 21 days. Ulcerations already present will heal within two weeks. Shrinkage of the lesion will usually follow if the treatment is continued for 30–90 days. If there is laryngeal involvement and stridor, this is usually dramatically relieved. If, on stopping the steroids, there should be any rebound of growth, a second or third course of hormone will usually be effective.

Alternate day steroid therapy may reduce the likelihood of steroid dependency and minimize complications. However, this remains unproved and several infants who had abrupt cessation of steroids (after 30 mg/day for 60 days) showed no evidence of adrenal difficulties. The search for the optimum dosage schedule deserves further study. Some aggressive hemangiomas will continue to enlarge while the infant is receiving 15 mg/day of Prednisone. We have not seen continued growth on doses of 20 or more mg/day.

Intralesional injections of Prednisone seem to have little advantage over systemic administration of the drug. Topical Betamethasone 17-valerate may be applied as a cream (for 6 hours daily) to capillary-cavernous hemangiomas with encouraging responses in very young infants when they show significant superficial dermal involvement.[21]

The original 7 infants in our 1967 report[23] have been followed for an additional 7 years (Figs. 3a to 3j). Although several have undergone later reconstructive surgery to remove residual noninvoluted vascular masses, or to correct deformities of features resulting from earlier



FIGS. 3h. Deep angioma was removed from the tip of the nose and the columella was constructed from dorsal nasal tip skin. The tumor in the upper lip has been removed and a mucous membrane flap is being inserted to replace the scarred vermillion. Two years later she has residual unresolved tumor in the left upper eyelid producing some degree of ptosis.

ulceration, none has had later recurrence of growth of hemangioma and none has developed late or persistent undersirable effects of the steroid therapy.

The mechanism of action of steroids on enlarging hemangiomas is still unclear, but Zweifach, Shorr, and Black[24] have shown that, in adrenalectomized rats, corticosteroids increased vascular sensitivity to circulating vasoconstrictive agents (Fig. 3e). Direct observations have also been made on the circulation in hamster cheek pouches with animals in adrenal insufficiency.[22] These investigators showed that intramuscular cortisone acetate produces arteriolar constriction and narrowing of the precapillary sphincters. In addition, they noted leukocyte coating of the endothelial walls. It seems not unlikely that rapidly proliferating blood vessels such as those seen in capillary cavernous juvenile hemangiomas may be highly susceptible to these mechanisms of steroid action.

Once the enlargement of a capillary cavernous hemangioma has been reversed and the family sees involution beginning, the surgeon and pediatrician will feel less pressure and more composure as they plan the future management of the remaining deformity and other symptoms (Figs. 4a and 4b). Areas on the face and neck that become ulcerated will usually leave sufficient scarring to require later plastic revision or skin grafting. A great variety of reconstructive procedures may be required for optimum correction of the resulting defects. In general it is wise to begin the major portions of this reconstruction before school age in order to minimize the adverse impacts of deformity on the child's self-image.

Our experiences with the use of CO_2 snow and liquid nitrogen to freeze capillary cavernous hemangiomas lead us to urge that these methods be abandoned. The surface scarring is hard to correct later and cold injury is relatively ineffective with the deeper portions of large lesions.

Irradiation Treatment of Hemangiomas

Gamma or beta irradiation therapy should never be used to treat any form of hemangioma. Indeed, Fost and Esterly[6] report "irradiation has been associated with damage to epiphyses, breasts, gonads, skin, lens and

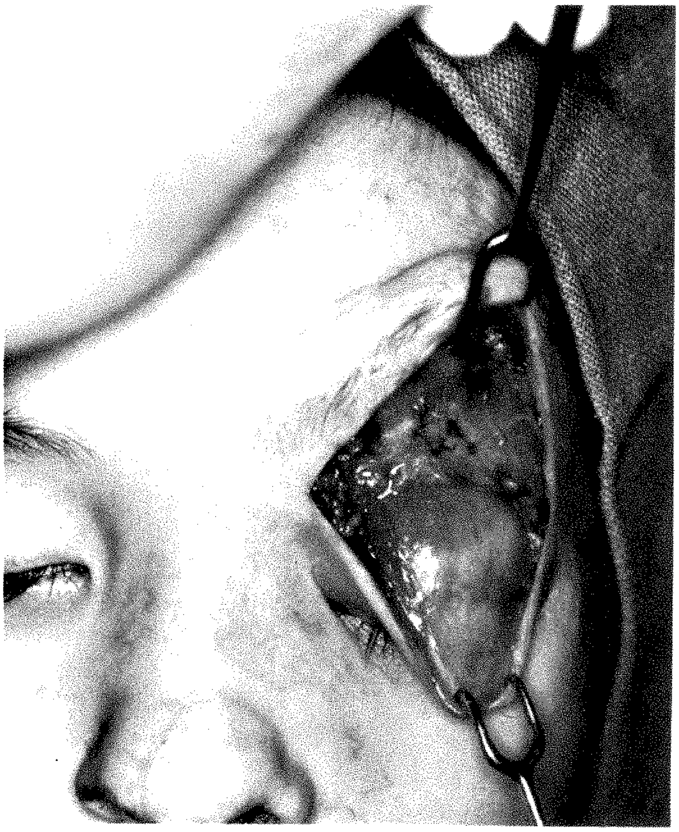


FIG. 3i. Massive deep angioma is still present in the left upper eyelid. At age 7 it was removed, taking care to preserve the adjacent levator palpebrae muscle fibers.

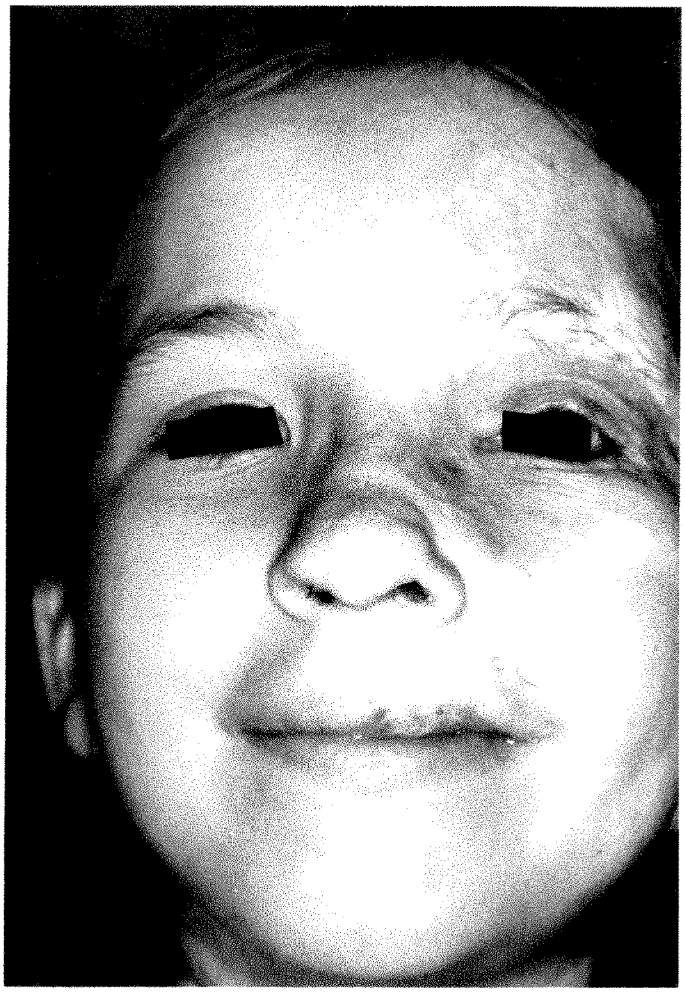


FIG. 3j. Present condition of the patient. She now needs only minor procedures to abrade and revise superficial scarring of nose, lip, and forehead.

thyroid, and in a large series yielded no better results than in untreated controls." They further point out that "the complications were ten times that in the untreated patients" (Figs. 5a and 5b).

There are numerous reports in the literature of carcinogenesis of the skin and deeper structures following the use of even light doses of gamma irradiation to treat hemangiomas in children (Figs. 6 and 7a–c). More recently Li, Cassady, and Barnett[13] have reported on 4,746 patients treated between 1946 and 1968 at the Boston Children's Medical Center by irradiation of hemangiomas during infancy. Despite the fact that the doses were all between 300 and 600 roentgens in air from a 50 cvp orthovoltage unit, there have already been three cancer deaths in this group with a mean followup of only 10 years. Two of these deaths were from lymphosarcoma and one from testicular teratoma (in this instance the irradiation included the testicle in the field of irradiation). Although the sample is still statistically small, one must be concerned about additional deaths from malignancy in this group of young patients in the years ahead. Li and Cassady[13] also point out "this was relatively low dosage x-ray and most (of the energy is) absorbed in the skin. Most induced skin cancers are curable and would not be ascertained by the methods of this study."

It is startling that in modern times a single hospital would continue to irradiate over 200 infants a year for a benign disease such as hemangioma!

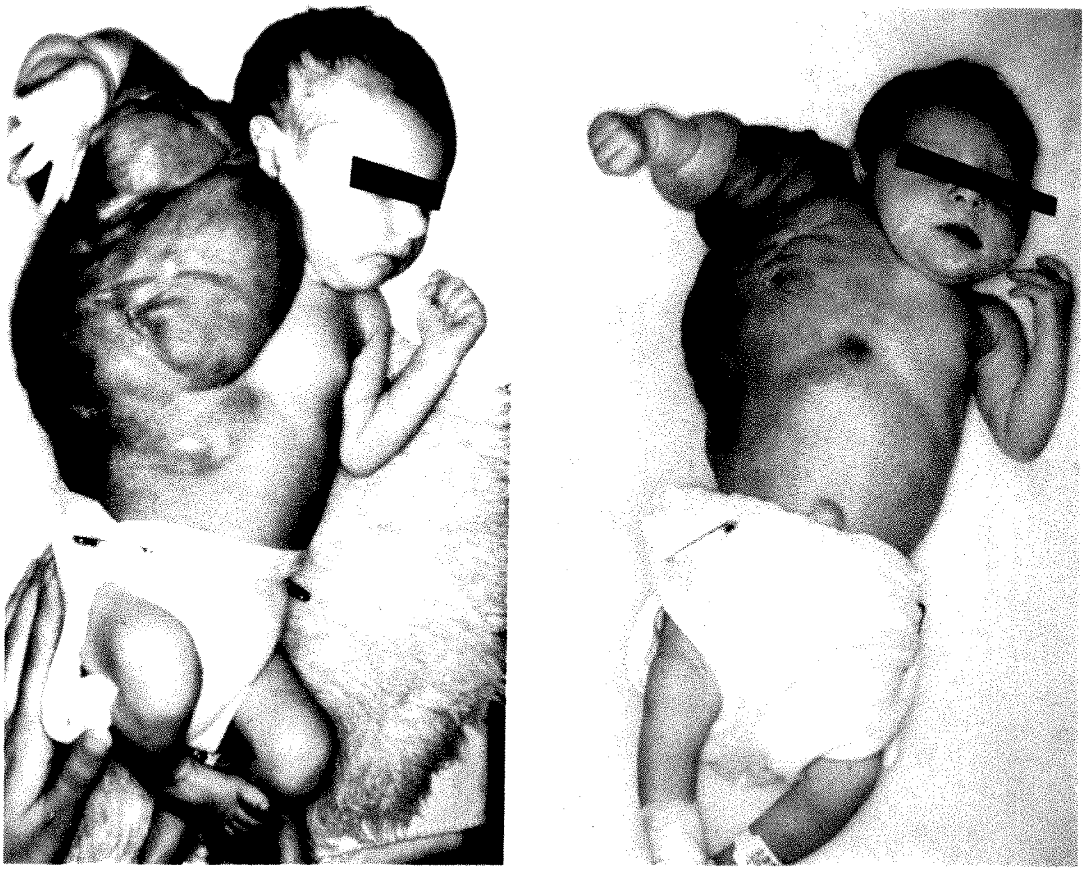
Disseminated Intravascular Coagulation (DIC) in Association with Giant Hemangiomas

Disseminated intravascular coagulation has been stated by Kwaan[11] and others to be "not a pathologic entity but a pathophysiologic intermediary mechanism of disease." This condition is associated occasionally with severe and uncontrollable bleeding in the postoperative period following surgical resection of portions of large hemangiomas. It seems probable that this condition is caused by hypoperfusion in a large hemangioma and that surgery may result in additional damage to the vascular endothelium of the remaining nonresected hemangioma. This leads to surface clotting, followed by the release of tissue thromboplastins into the circulation of the patient. Intravascular clotting then appears to produce microthrombi in innumerable small vessels throughout the body. Thrombi do not appear to form in the large blood vessels. The microthrombi cause a removal of platelets and fibrinogen from the circulation. Also factors II, V, VIII, X, and XII may be reduced in the circulating blood. As a result of these subtractions of elements important for clotting, bleeding may occur and may respond very poorly to treatment with fresh whole blood or platelet transfusions.

The fibrin clots formed in patients with DIC tend to cause the release of plasminogen activator from the endothelium in amounts 5 and 10 times above normal. This in turn causes a secondary fibrinolysis at a rate that exceeds the patient's ability to synthesize new fibrinogen. The breakdown products of this secondary fibrinogen degradation have large molecular weights (50–270,000) and at least 4 have been found to be effective antithrombin factors. These degradation products (FDP's) thus tend to further increase bleeding.

In DIC, the kidneys are commonly involved. Oliguria and hematuria may result from microthrombi forming in the glomerular capillaries. Patients may also have hemoptysis, adrenal failure, pancreatitis, or gastrointestional bleeding. Some patients with DIC will show hemolytic anemia and reduced plasma haptaglobins.

DIC may occur with a variety of disorders and all of these have the common denominator of being capable of producing procoagulants. They include such clinical con-



FIGS. 4a and b. (left). Massive rapidly growing capillary-cavernous hemangioma in newborn infant with associated thrombocytopenia. Bleeding problems and poor nutrition of the infant made the prospects of surgery formidable. (right) Ten days after the initiation of steroid therapy, the infant had shown this response. Further regression occurred over a period of months, making surgical excision of the residual masses a practical matter. Steroid therapy has proved most effective in the most massive lesions where effective treatment is most urgently needed.

ditions as massive red cell hemolysis, placental separation in pregnancy, massive burns, fat embolism, shock, pulmonary embolism, some allergies, as well as massive hemangiomas.

Jona[10] has reported the case of a 16-year-old boy with 19 hemangiomas, melena and anemia. After each attempt to resect one of these hemangiomas, he experienced severe disseminated intravascular coagulation and massive bleeding. He responded well to treatment with heparin (3000 international units q. 4 hours intravenously) and aspirin (300 mg orally q. 6 hours).

Heparin interferes with clotting and therefore decreases the tendency to further disseminated intravascular coagulation. Warfarin has not been found to be very effective in this condition. EACA (episilon-aminocaproic acid) may be helpful if fibrinolytic activity is excessive. It must be used with care as it may, however, cause serious thrombotic complications. When properly treated with heparin, patients with DIC should show a rise in fibrinogen and platelet levels within 24 hours. Surgical removal of the angioma should be completed while the patient is still on heparin.

Surgeons operating on any massive hemangioma must be on the lookout for the development of DIC and prepared to treat it appropriately. *Complete* resection of a hemangioma is less likely to initiate a bout of acute DIC than is *subtotal* removal of the endothelial mass.

Type 4: Arteriovenous Fistulae

Congenital arteriovenous fistulae differ from traumatic A-V fistulae in several important particulars. The communications are usually quite small in the congenital variety but they may be several hundred in number. Traumatic fistulae are usually one or two in number and may have larger diameters leading to the more typical type of cardiac enlargement and right-sided heart failure. *Congenital* A-V fistulae do not usually produce cardiac failure but may on occasion do so if the shunting is uncontrolled. There are two types of congenital A-V fistulae:

Arterial hemangiomas: These lesions are usually diagnosed clinically because of an elevated skin temperature, a rather bright red color (in some instances resembling a port wine stain), but with a steady tendency to progression and enlargement of the part. There is often a definite pulsation or thrill and bruit. Arterial hemangiomas may be apparent in very early childhood and enlarge at irregular rates until adult life. In females, the development of pregnancy may precipitate marked

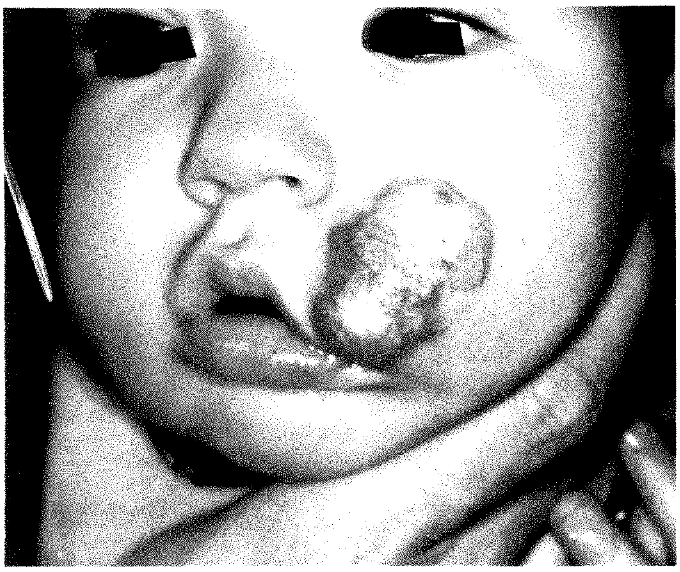


FIG. 5a. This child has a capillary-cavernous juvenile hemangioma of moderate size. Although the surface of the hemangioma showed some sclerosis, the deep mass within the cheek continued to grow. The physician treating this child recommended "mild" doses (800 rads total dose) of radiotherapy.

further enlargement with serious hemorrhage. Bone erosion and cartilage involvement may be seen. Arteriography will often reveal many tiny shunts within the local region.

Treatment: Peripheral ligation of vessels, sclerosing solutions, x-ray therapy, freezing, electrodessication, injection with boiling water, and many other modalities have all been tried unsuccessfully in efforts to control these alarming lesions.

About the only effective method to prevent progression of the vascularization is the *surgical resection of all of the A-V shunts* within these congenital lesions (Figs. 8a to c). When the fistulae are relatively limited in locality, this may be possible with an effective and permanent control. If, however, a significant number of shunts must be left behind, one can anticipate a slow, but relentless, reappearance of the warm pulsating mass with the return of abnormal hemodynamics leading to, in some instances, right heart failure.

In 1931 Brooks[2] described the use of small fragments of autogenous muscle for embolization of the arteries leading into congenital A-V fistulae. More recently, Luessenhop,[15] Cunningham and Paletta,[4] and Bennett and Zook[1] have reported further encouraging experiences with this technique. Small muscle fragments approximately ½ cm in diameter are inserted by arteriotomy into the major feeder vessels leading into the fistulae. The muscle is flushed into the distal artery with saline and x-rayed with the aid of radiopaque dye to determine location of the emboli, following which the vessels are ligated. Reduction in the size of the A-V hemangioma has been accomplished in some patients by this method.

Recently, Longacre, Benton, and Unterthiner[14] have employed the use of small silicone spheres as intravascular emboli in a patient with A-V fistulae. They report their patient still improving 4 months after insertion of 18 spheres between 1 and 3 mm in diameter into the distal stump of the external carotid artery.

We have used embolization as an adjunctive procedure

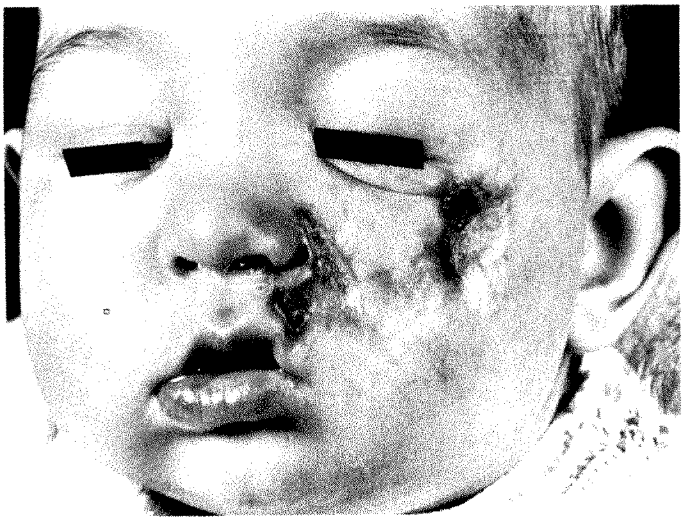


FIG. 5b. Although the hemangioma responded to gamma irradiation, the ulceration, scarring and deformity of the cheek 3 months later is awesome. Irradiation should never be used in the treatment of hemangiomas.

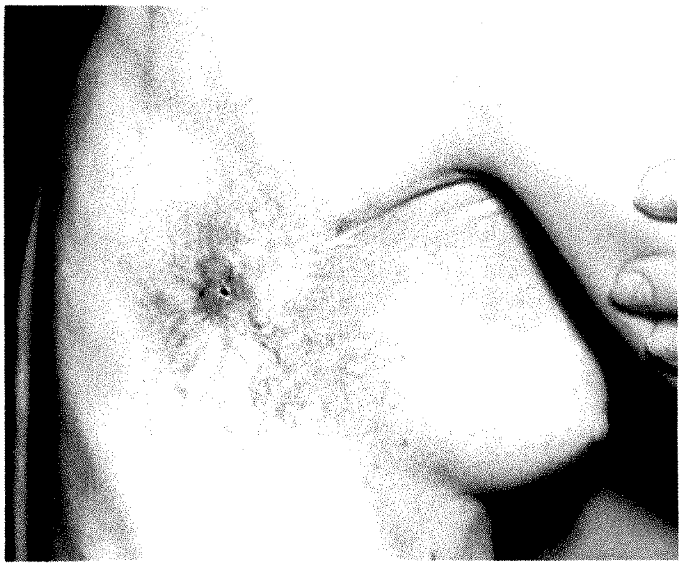


FIG. 6. Eighteen-year-old girl with a 1 cm capillary hemangioma of the chest wall treated in infancy by a 20-minute application of a radium plaque. The angioma disappeared but irradiation telangiectasia and scarring appeared within the skin. The ribs of the right hemithorax developed to less than one half the size of those on the left. The right breast is less than one half the size of the left breast, and a biopsy taken of the small ulcer shown revealed "squamous carcinoma." Many similar cases have been reported in the medical literature.

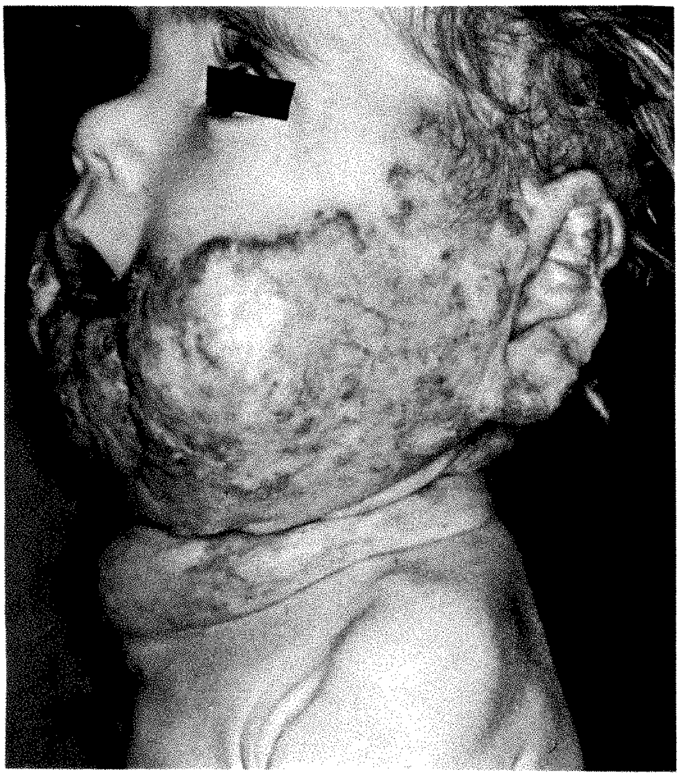


FIG. 7a. This 2-month-old infant with a massive capillary-cavernous hemangioma was losing weight, had severe stridor from laryngeal involvement, and had developed ulceration of the lips and hyperthermia. Irradiation therapy had been tried in desperation, but with minimal response. Emergency tracheostomy had to be performed directly through the bulky vascular tumor in the deep anterior neck. Intubation through the involved larynx seemed to hazardous.

with A-V fistulae in an effort to reduce size and minimize bleeding at the time of surgical resection. The use of hypotensive anesthesia and preliminary control of major arterial trunks have added to the safety and effectiveness of surgical control of the congenital A-V fistulae.

Hemangiomatous giantism: In some instances, congenital A-V fistulae seem to be associated with marked regional giantism of the involved part. Most often this involves an extremity but may involve the lower jaw, lip, or some other facial feature. There is usually a purple discoloration of the skin with marked enlargement of the underlying bones and soft parts. X-ray may reveal radiolucent areas in the shafts of long bones where these shunts exist. Bleeding is not uncommon and, indeed, ischemic ulceration may occur in an extremity as a result of the inefficient perfusion of distal parts of that extremity in the presence of multiple large shunts, more proximally located. Attempts to control enlargement or bleeding by proximal arterial ligation will usually lead only to further distal ischemia with pain and gangrene often developing. In the presence of cardiac enlargement, amputation of the part may be the only practical treatment.

Type 5: Cirsoid Angioma (Racemose Aneurysm)

A relatively uncommon form of hemangioma may be composed of large wormlike clusters of venous tributaries with purple discoloration of the overlying skin and a tendency of the lesions to become tense and swollen when the venous outflow to the region is obstructed. These may be seated quite deeply and at times the walls of these angiomas will contain many fine cutaneous nerves that may produce significant pain when the lesions become engorged.

Cirsoid angiomas may enlarge slowly. They do not involute and respond only to surgical excision. Usually staged procedures in combination with appropriate reconstruction will produce the maximum relief.

Lymphangiomas

Although this paper will not deal exhaustively with the treatment of lymphangiomas, it is essential that several important distinctions be made between hemangiomas and lymphangiomas in regard to clinical manage-

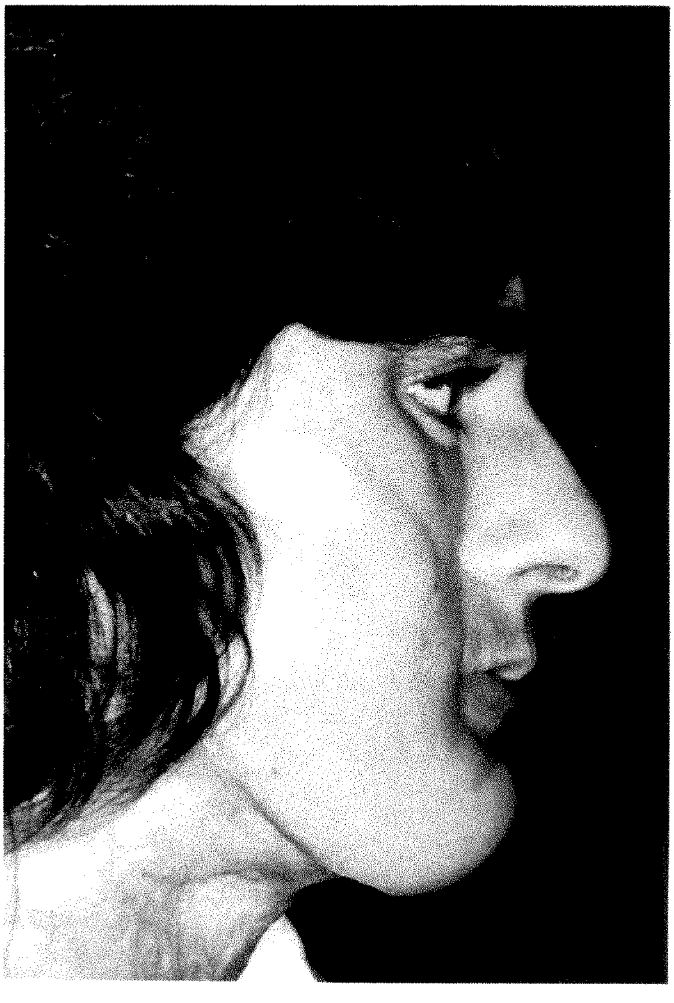


FIG. 7b. Bone graft has been supplied to elevate the right eye and flap has been fitted into parotid region. Chin pad is unduly prominent.

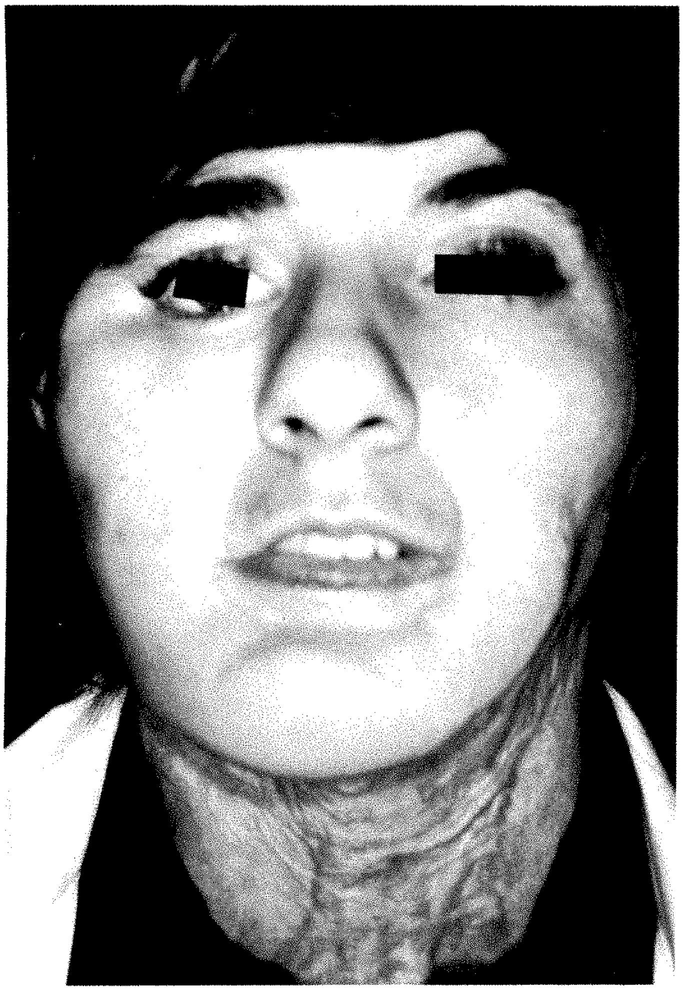

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FIG. 7c. Present condition shows facial reconstruction largely completed and now awaiting a cosmetic overlay graft to provide a smoother surface texture to the grafted anterior neck. Much of the reconstruction over the years in this young woman was required to repair the effects of gamma irradiation on bone and soft tissue.

ment. *Contrary to widespread medical opinion, lymphangiomas and hemangiomas are seldom intermingled in the same patient.* Although some lymphangiomas do have a dark red color suggestive of hemangioma, this is due to different pathology, involving blood pigment in stasis within lymphatic channels, unlike the red tones produced by the rapidly circulating blood in the capillaries and larger vessels of a hemangioma.

Like hemangiomas, lymphangiomas may be diffuse or cystic in nature and, in the absence of obvious blood pigment within the sinusoids, it is difficult for a pathologist to distinguish the endothelium of these two lesions. Despite this, they are entirely different from the standpoint of prognosis, clinical symptoms, and methods of treatment.

Lymphangiomas may be found in tissues quite deep to the skin. Very commonly, in the head and neck region, they also involve the skin, producing a light brownish pigmentation, frequently small keratotic papillomas and occasionally drainage of clear yellow lymph from one of these skin excrescences. When the lymphangioma reaches the surface of any body cavity that is lined with mucous membrane or serosa, it produces multiple tiny vascular tufts that are pale in color, and each with a single pink center. This gives mucous membrane a typical appearance that is pathognomic for the diagnosis of lymphangioma.

At times, lymphangiomatous enlargement of soft tissues may be accomplished by localized giantism of that part of the body.[5] This symmetrical enlargement of the part may involve soft tissue, bone, teeth, or indeed any structure. The pattern of enlargement often reflects the peripheral sensory nerve distribution to that region. In many, but not all, instances of localized giantism, the careful examination of histologic sections will reveal plexiform neurofibromatosis to be a part of the local picture.

When left untreated, the natural history of the localized lymphangioma is usually one of very slow enlargment, accompanied after a period of months or years by the tendency to recurrent episodes of cellulitis and ascending lymphangitis. This may become more frequent with the passage of time producing episodes of severe systemic illness and fever. These bouts of infection leave the lymphangioma increasingly indurated. When a lymphangioma is located in the region of the oral cavity or neck of an infant, respiratory obstruction is not uncommon and may even be fatal. In the facial region,

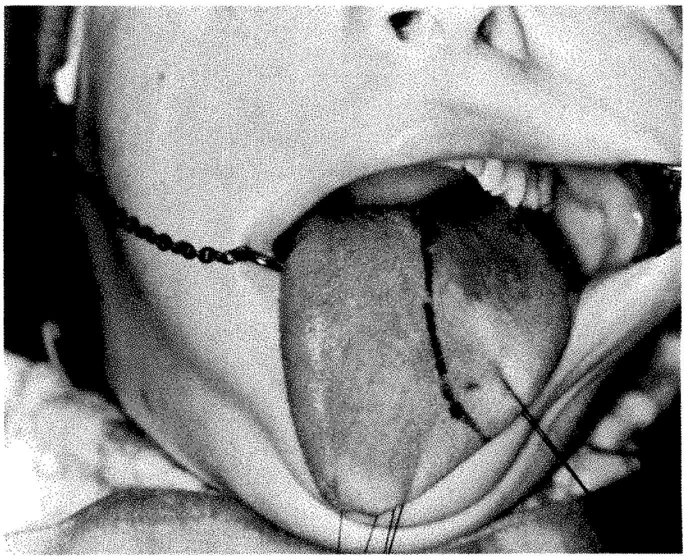

FIG. 8a. This 16-year-old girl had enlarging pulsating, warm, congenital A-V fistulae involving the base of the left tongue. Alarming, bleeding had occurred on two occasions. The lesion was first noted approximately 3 years before.

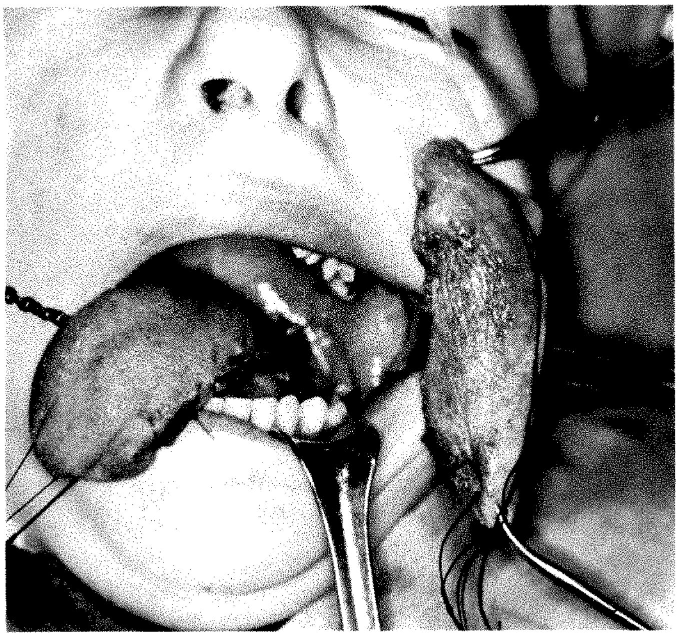

FIG. 8a. Arteriograms shows the shunting confined to the left half of the tongue. A surgical resection of one third of the tongue was carried out intraorally, after obtaining control of the carotid arteries. A pharyngeal flap was used to close the base of the tongue.

deformity often brings the patient to the attention of the plastic surgeon. Lymphangiomas do not spontaneously involuate in the manner of juvenile capillary hemangiomas but the tendency to growth becomes less noticeable after about 17 or 18 years of age.

Treatment: The lymphangioma is almost totally resistent to any form of irradiation of cryotherapy. Although sclerosing agents have been used to reduce the size of cystic hygromas, it is a relatively unsatisfactory method of management and greatly complicates any later surgery that might be required to reduce the mass.

In the vast majority of instances, surgical excision is the only effective method of controlling the lymphangioma. Since the involved tissue very rarely becomes malignant, it is usually safe to retain some portions of the affected area for use in local reconstruction. It is not essential that the entire lymphangioma be removed in order to control or prevent further symptoms from developing. When localized giantism is present with a lymphangioma, we prefer to perform longitudinal reductions of the massively thickened sensory nerves supplying the enlarged region. This is done at the earliest practical date in the hopes of further reducing stimuli to overgrowth of the part.

The patient with a massive lymphangioma presents one of the most difficult and complex problems seen by plastic surgeons and may require an extensive gamut of reconstructive techniques to eliminate deformity and restore function.

General Principles in the Treatment of Angiomas

The most valuable methods currently of value in the treatment of the various clinical varieties of hemangioma include the use of: 1) *Observation* to await involution in the case of neonatal staining or the smaller circumscribed juvenile strawberry capillary hemangiomas. 2) "*Heavy dose–short course*" steroids (or occasionally sclerosing agents) to accelerate involution is the principle treatment approach to growing juvenile capillary, or capillary-cavernous hemangiomas. 3) *Intermittent compression* of a hemangioma is of value when there is associated thrombocytopenia. Subsequent surgical excision of the tumors with plastic closure may often be required. 4) *Surgical excision in combination with skin grafts or pedicle flap repair* remain the most valuable treatment approaches for intradermal capillary hemangiomas, arteriovenous fistulae, or cirsoid hemangiomas. 5) *Medical tattooing and cosmetic cover-up creams* of port wine stains have both been disappointing. Skin graft replace-

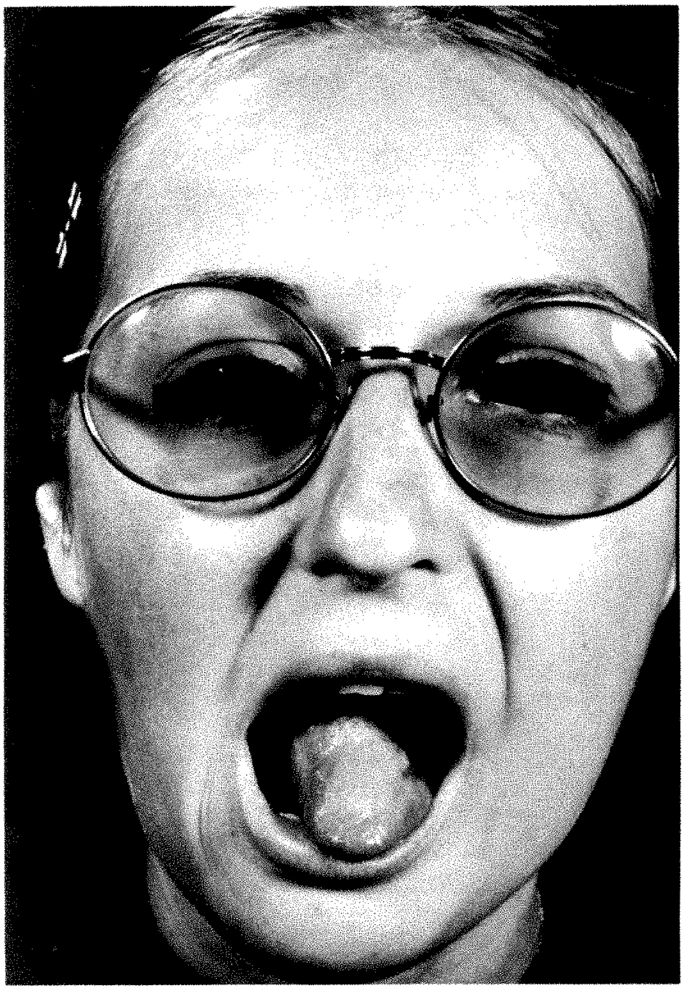

FIG. 8c. Appearance of tongue two years later with some tipping of the base of the tongue. Excellent speech and no problem in swallowing.

ment of port wine stains is becoming more effective with better graft techniques and the use of skin from donor sites with "blush" capabilities. 6) There is very little indication for the use of CO_2 snow, liquid nitrogen, or electrodessication. 7) Any form of irradiation is always contraindicated in the treatment of hemangiomas! 8) Lymphangiomas usually require staged surgical resection and reconstructions. They do not involute and portions of tissue containing the abnormal lymphatic network may be used in the reconstructions.

Comment

Hemangiomas have been defined and a classification has been proposed which combines the essential features of prognosis and optimum treatment methods. Treatment of each major variety of hemangioma has been outlined and special emphasis has been placed on the use of systemic steroid therapy as an invaluable aid in the management of the massive juvenile capillary-cavernous hemangiomas of infancy.

Some consideration has been given to the surgical treatment of port wine stains and other intradermal hemangiomas. Current approaches to the management of congenital arteriovenous fistulae are outlined.

Major complications of gamma and beta irradiation therapy are demonstrated to support the position that they are unwise and contraindicated methods of treatment for all forms of hemangiomas.

More attention should be paid to the psychic impacts of deformities resulting from hemangiomas. In that regard, plastic surgical techniques can be used more effectively and applied at younger ages than has been the custom in the past.

Several important distinctions have been made between lymphangiomas and hemangiomas in regard to prognosis and treatment.

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DISCUSSION

DR. STEPHEN R. LEWIS (Galveston): Dr. Edgerton does not like Covermark for covering the port wine stain. I'm not sure that his skin grafts are that much prettier than a port wine stain covered with good cosmetics. We have found that the adult male, or most males, will not use Covermark, but females use it, and use it relatively well.

Our skin grafts usually are not as mobile as that skin that he has removed, and I think our end result with cosmetics is usually a little bit better than our skin grafts, although we have skin-grafted a number.

So many times when we have excised the port wine stain, we see a recurrence of the lesion at the border when we're well around the primary lesion. I wonder if Dr. Edgerton has had this same complication or problem with his grafts.

Staged excision in many hemangiomas, with local rotational flaps, if possible, at least on the face, are in our hands a little bit easier and better to use than skin grafts, although a skin graft from the neck does work fairly well.

We have had problems with a number of these cases we have followed over the years that we thought we resolved, and then get rather rapid growth in the patients' thirties or forties especially during pregnancy. I'd like to ask whether steroids in the adult group have been tried by his team, and if they have had any good results. They have not worked well for us.

Lastly, we think very strongly that by using the new method of liquid nitrogen, with probes, in freezing of most hemangiomas of the cavernous type, we have developed good results in a high percentage. Usually, we ligate the external carotids in those intraoral lesions, and then follow it with the nitrogen probe and freezing; and I think this may give us a much better result.

I agree wholeheartedly with his statements on radiation. I think that radiation has caused much more damage than the hemangioma of almost any kind. In one case we had a rather disastrous experience. After ligating the external carotid about 20 years ago on one side, a year ago we ligated the other one, when she had developed massive recurrence in her tongue, buccal mucosa and the cheek, with bleeding, so that we ligated the other external carotid. She then lost about half of her skin over the occiput down to and including part of the bone. Why, we don't know. There is no known reason for the tissue loss, but it's caused us a good deal of trouble.

I do want to congratulate Dr. Edgerton on excellent results with a tremendous number of cases. I would caution that a large percentage of the strawberry marks, if we let them alone and watch them, as Lister said years ago, 95% will disappear without the need of surgery. I do think there is a reason for this disappearance, and we should wait for it in a higher percentage of our cases.

Dr. J. Alex Haller, Jr. (Baltimore): I would like to call attention to a complication of cavernous hemangiomas in children which we have seen in the last several years which Dr. Edgerton did not include in his discussion, and perhaps will mention in closing: This is the problem of platelet trapping in some of these large hemangiomas in children. This process results in thrombocytopenia, with major purpura and even excessive hemorrhage into those tissues surrounding the lesion, as well as from other parts of the body.

This is a particularly terrifying problem. I want to emphasize it this evening because the histologic findings in the biopsy of some of these lesions may be quite misleading. The pathologist may give you the frozen section report that this represents a hemangioendothelioma which is malignant in nature; in other words, a sarcome of these tissues.

In children a malignant hemangioendothelioma is practically never found. These represent, instead, very active cellular proliferation of the hemangioma, and this activity apparently is related to potential trapping, or adherence, of platelets within the interstices of these vascular masses. They can grow very rapidly. I would like to underline what Dr. Edgerton said about early use of steroids, because we have had some dramatic results in controlling the growth potential of these lesions in children with early, massive steroid therapy.

Two particular cases that we have treated recently were dramatic examples; one, a very large cavernous hemangioma of the buttock of a four-month-old child, would have required practically a hemipelvectomy, and the other in the knee of a little girl of three years of age, which would have required a hip disarticulation. These radical procedures were both recommended by the initial surgeons who saw these children.

Fortunately, they were subsequently biopsied and treated with steroids; both have regressed and, I think, will ultimately disappear. I wanted to emphasize this as one of the rarer but serious complications associated with large cavernous hemangiomas.

Dr. Richard C. Miller (Jackson, Mississippi): I rise only to mention some of our experience with visceral hemangiomas, which may be every bit as troublesome as the massive cutaneous and limb hemangiomas which Dr. Edgerton mentioned.

These patients may present with an abdominal mass, (slide) or sometimes they present with hemorrhage. There is little problem, as with this child, when the hemangioma is on the edge of the liver, and it can be resected easily. However, sometimes they are central in the liver, or on occasion they may present with massive hemorrhage. (slide) This child had rectal bleeding from colon involvement; had a pelvis full of hemangioma; and also presented with gross hematuria. He required exploration of his bladder and oversewing of these large hemangiomas inside the bladder. (slide) You are now looking into the bladder, and can see the ulcerated hemangiomas. Eventually the child required rather radical treatment—namely, a total cystectomy. (slide) The pathologic specimen illustrates that the entire bladder is completely infiltrated by hemangioma.

Visceral hemangiomas may or may not regress. Occasionally a child is seen with liver calcifications and we presume he did have a hemangioma. On the other hand, visceral hemangiomas may progress, and require quite vigorous management.

Dr. Claude C. Coleman, Jr. (Richmond): I congratulate Dr. Edgerton on his masterful presentation, but take exception to including a condition as highly malignant clinically, as highly progressive and destructive, as poorly defined roentgenologically, or using any other means of diagnostic acumen, as the congenital arteriovenous malformation.

Our studies, which have been considerable, indicate that about 40% of these tumors are bilateral. We have never been able to delineate the magnitude of the three-dimensional extension of such tumors roentgenologically, because of the vestigial rests, which don't open up until one starts ligating vessels. We feel that this vascular anomaly belongs in a class by itself. Otherwise, I agree with most of what Dr. Edgerton said.

Dr. Milton T. Edgerton (Closing discussion): Dr. Haller, in the manuscript we do have a considerable section devoted to the problem of the cavernous hemangioma with thrombocytopenia and the development of disseminated intravascular coagulopathy. It's a special and frightening problem.

We have currently one patient now in the hospital that my colleague, Dr. William Futrell, has been struggling to help. This is a young woman, 19 years old. Dr. Claude Coleman saw her at an earlier point in his career when she was only three years old. At our hospital she has just gone through an operation requiring 184 units of whole blood transfusions in just over 72 hours! At present it would appear that she's going to recover. Her disease consisted of a massive cavernous hemangioma of the chest wall, abdominal wall, groin, and lower extremity which was bleeding continuously as a result of D.I.C. with fibrinogen and platelets trapped in the giant angioma.

Paradoxically, heparin was the medication that helped bring the preoperative fibrinogen levels back toward normal in this patient making surgery possible. There's more about D.I.C. in the complete manuscript.

I was delighted to hear that Dr. Haller has also had good results with steroids in treating massive juvenile hemangiomas.

Dr. Lewis correctly makes the observation that most plastic surgeons still recommend some form of makeup to cover many port wine stains. I would make two points to underline my personal disenchantment with these products. Like Dr. Lewis, we have had ablutely *no* success in getting male patients to use make-up of any kind. Don't waste your time! They won't wear it. It shouldn't even be suggested.

It is true that with encouragement some women will use makeup (especially if you don't offer them any surgical alternative). Most of them don't like it, and years later many of them will again seek surgery. They all tell us the same thing: "Doctor, this makeup looks okay, but it takes constant effort, it's hot, and it does nothing to relieve the sense of deformity."

I agree with Dr. Lewis that skin graft replacement of port wine stains is sometimes not a bit better looking than the result with Covermark; but, even so, many patients state they would rather have the skin graft. One stated, "The scars from the skin grafts are the surgeon's fault. They are not deformities I was born with so I am not embarrassed."

Sometimes the apparently normal skin at the margins of the port wine stains will turn red and form a new rim of capillary hemangioma when you resect all of the clinically involved skin and replace it with a graft. A new area of port wine stain seems to appear in a previously uninvolved area of the skin. Dr. Ferris Smith and Dr. Staige Davis pointed this out many years ago. The only clue we have to the cause of this phenomenon is that it seems to occur in areas of skin that experience maximum tension when the wound is closed after excision of all or part of an angioma. This additional tension may open up vascular filling in the dermis of an occult area (within the predetermined pattern of the angioma) of the vascular anomaly.

We have tried steroids for treatment of *adult* hemangiomas. We have tried them on all age patients with lymphangiomas; and we have tried them to control A/V fistulae. We have had *no* therapeutic success with any of these groups.

I have had limited experience with the liquid nitrogen probe. We have used it only a few times. The results showed skin with uneven scarring and lumpiness. If the technique can be developed to give uniform thrombosis, it may yet prove of value.

Pregnancy does make some angiomas progress, particularly congenital A/V fistulae. They enlarge markedly, and frightening hemorrhage may occur during the later months of pregnancy.

Many times we should wait for resolution of strawberry marks, but my principal plea tonight is that *each hemangioma* must be individualized. Sometimes surgical excision is simple, quick, effective, and may be the ideal treatment for the child.

Dr. Miller added some valuable comments about visceral hemangiomas which I appreciate, and his experience with these lesions will aid all of us.

Finally, Dr. Coleman, I agree that the A/V fistula embodies *all* of the bad things you said about it. In my opinion the A/V fistula is worse than cancer. I don't mean to suggest that it's like all other hemangiomas even though the pathologist will call it an "angioma" on reviewing the slides. My plea tonight is simply that we must distinguish the A/V fistula from all other varieties of hemangioma if we do call it a type of hemangioma.

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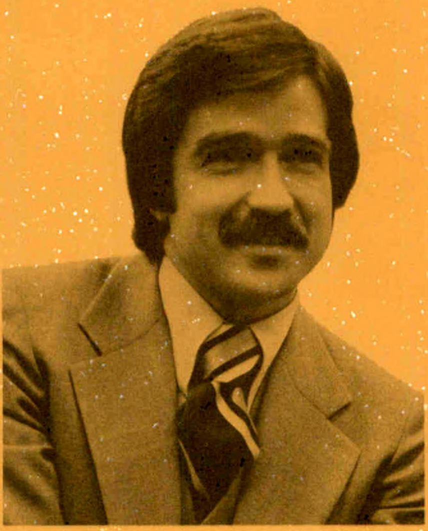

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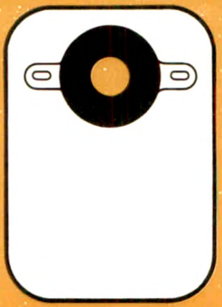

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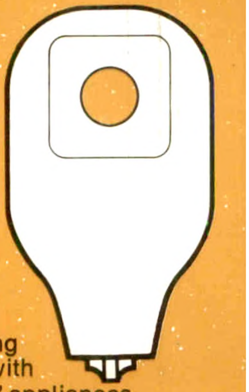

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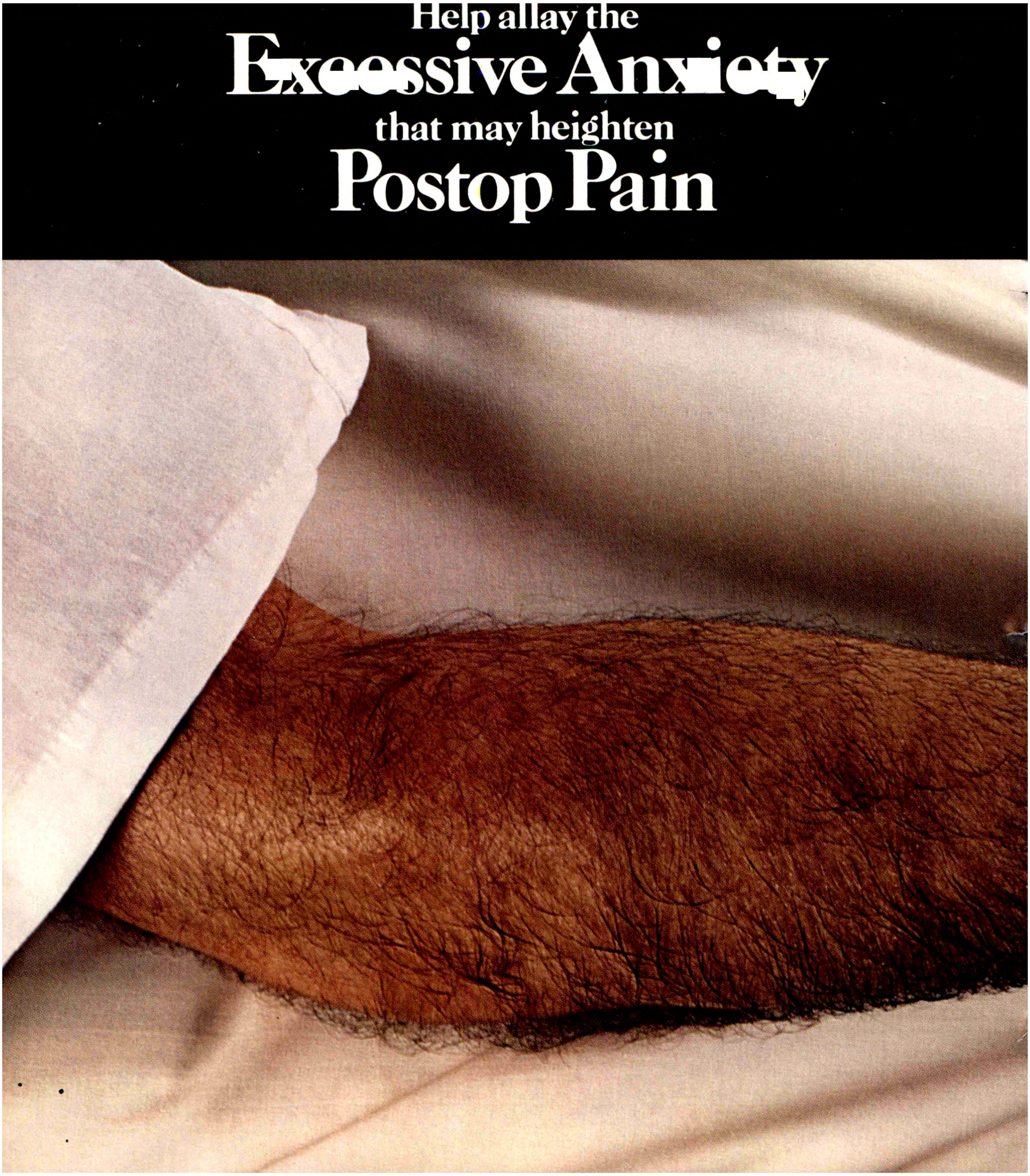
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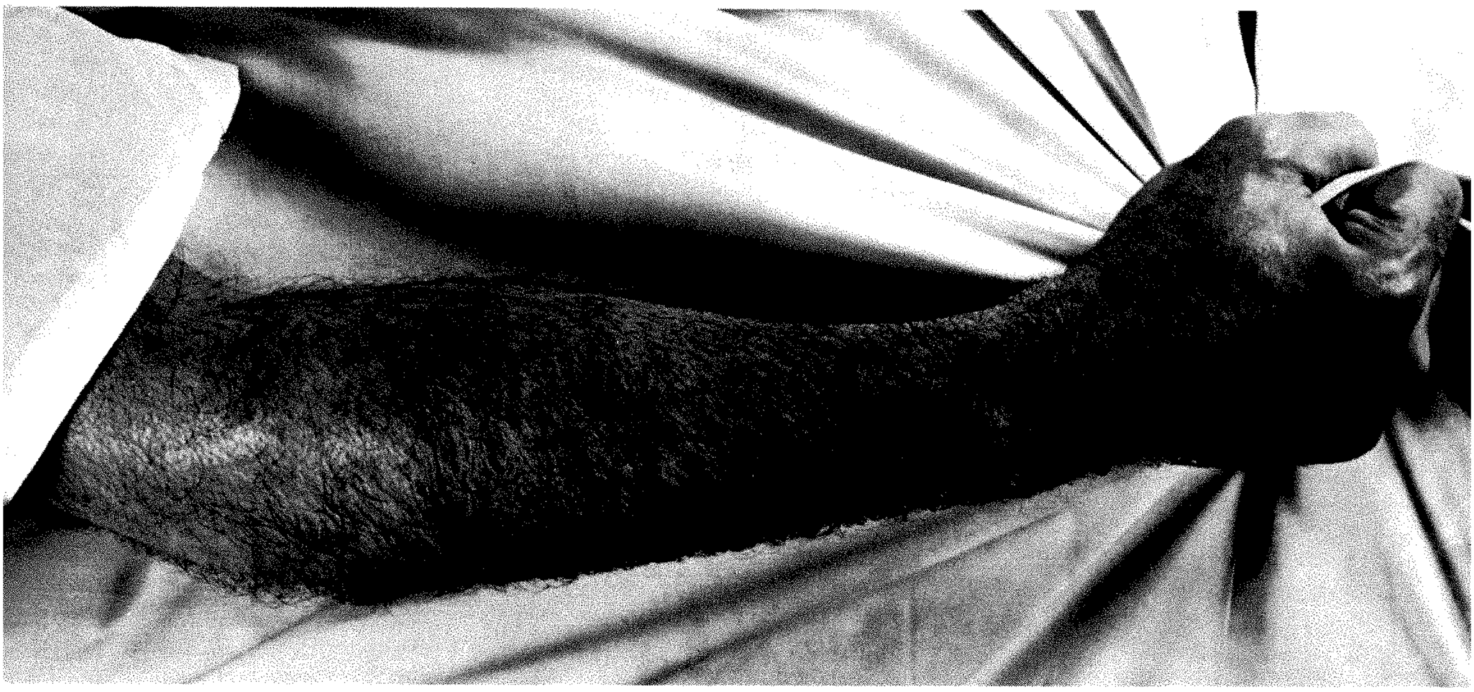
Vials and Isojects®

helps relieve the anxiety associated with postoperative pain

may enhance narcotic effect

offers proved antiemetic action



Brief Summary
VISTARIL® (hydroxyzine hydrochloride) Intramuscular Solution
For Intramuscular Use Only

Contraindications: Hypersensitivity to hydroxyzine. The solution for intramuscular use *must not* be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: *Hydroxyzine may potentiate the action of central nervous system depressants such as narcotics and barbiturates.* In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used.

•Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in ord to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults a older children, and only with caution to avoid radial nerve injury. Injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid intravascular injectio

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg./ml.-10 ml. vial; 50 mg./ml.—2 ml. and 10 ml. vial; Isoject®, 25 mg./ml. and 50 mg./ml., 1 ml. fill; 100 mg./2 ml., 2 ml. fill.
Military Depot: NSN 6505-00-052-1367 (50 mg./ml., 10 ml. vial)
VA Depot: NSN 6505-00-052-1367B (50 mg./ml., 10 ml. vial)

More detailed professional information available on request.

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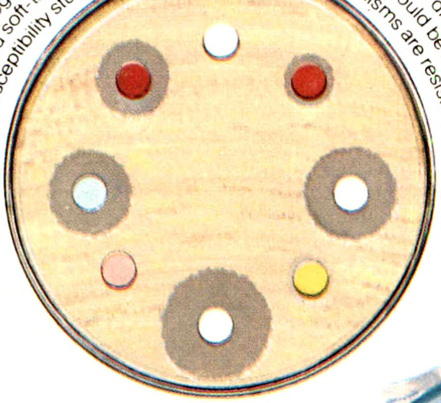
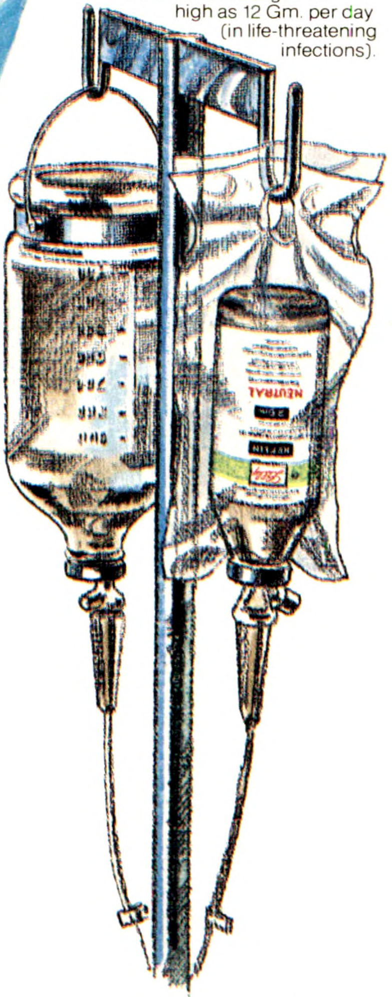
Appropriate cultures should be taken, but Keflin® (cephalothin sodium, Lilly) may be started before susceptibility results are obtained if you suspect the causative pathogen is one of the susceptible organisms for which the drug is indicated in skin and soft-tissue infections.* Other antibiotic therapy should be instituted if susceptibility studies show that the causative organisms are resistant.

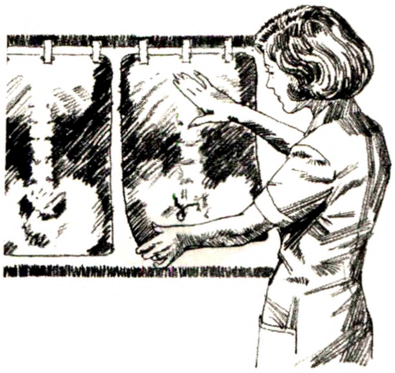


In the immunosuppressed patient, usual clinical signs and symptoms of infection may be missing or not clear. Hence, diagnosis and initiation of proper therapy become most urgent.

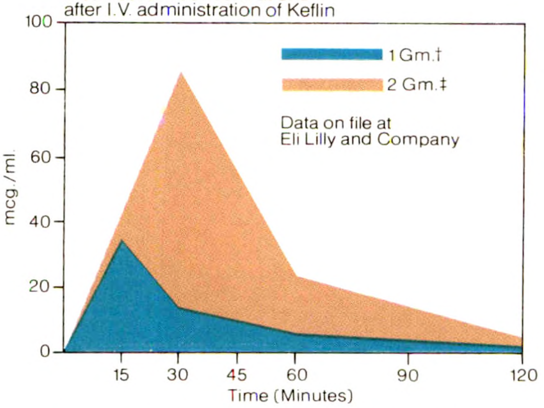
An initial loading dose of 1 to 2 Gm. of Keflin may be given regardless of the patient's renal status. Patients with impaired renal function should be placed on a reduced dosage schedule. Usual doses in such individuals may result in excessive serum concentrations.

Keflin may be administered I.V. or I.P. in dosages as high as 12 Gm. per day (in life-threatening infections).





Mean serum concentrations after I.V. administration of Keflin



†Administered to six patients by rapid I.V. infusion.

‡Administered to ten patients over a thirty-minute period.

*Skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*.

Please see opposite page for summary of prescribing information.

In serious skin and soft-tissue infections*

OFTEN USEFUL WHEN MOST NEEDED

As you know, skin and soft-tissue infections,* including peritonitis, may progress with alarming rapidity in patients with impaired host defenses...even to the point of becoming irreversible. Keflin can often be useful before the infection becomes irreversible...exactly when it is most needed.

Eleven years after its introduction, Keflin continues to be effective against most strains of gram-positive and gram-negative organisms commonly implicated in serious skin and soft-tissue infections.* Therefore, when you suspect that the pathogen involved is one of the susceptible organisms for which the drug is indicated in skin and soft-tissue infections,* you may begin therapy with Keflin even while results of susceptibility studies are pending...and thus save precious hours for the patient. Keflin may be administered to infants and to patients with reduced renal function.

Keflin should be given cautiously to penicillin-sensitive patients.

It is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

*Skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Esch. coli*, *Pr. mirabilis*, and *Klebsiella*.

Keflin® 2 Gm.† in 100-ml. ampoule
cephalothin sodium
Neutral
for Injection

†Equivalent to cephalothin.

Brief Summary.
Consult the package literature for prescribing information.

Indications: Keflin® (cephalothin sodium, Lilly), Neutral, for Injection, is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*

Bone and joint infections caused by staphylococci (penicillinase and nonpenicillinase-producing)

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy—Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side-effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: Maculopapular rash, urticaria, pain, induration, tenderness, elevation of temperature, reactions resembling serum sickness, anaphylaxis, eosinophilia, drug fever, neutropenia, thrombocytopenia, hemolytic anemia, thrombophlebitis, transient rise in SGOT and alkaline phosphatase, rise in BUN, decreased creatinine clearance, and a positive direct Coombs test have been reported. [111475S]

Additional information available to the profession on request.

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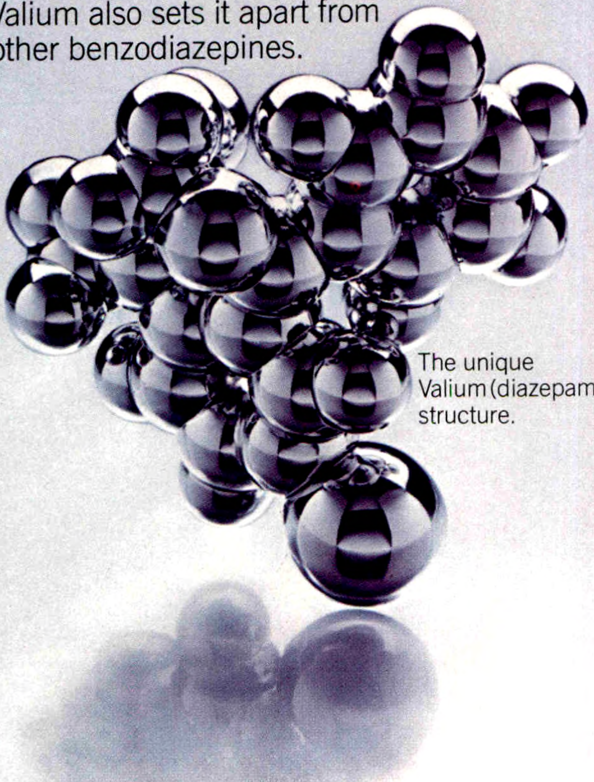
No other benzodiazepine on any hospital formulary

Valium (diazepam) is the one benzodiazepine with three clinically useful pharmacologic properties. Pharmacologically, Valium has potent psychotherapeutic, skeletal muscle relaxant and anticonvulsant properties. Extensive studies have demonstrated that all three of these properties are *clinically* useful. Other benzodiazepines may show similar properties in the laboratory, but *clinical* usefulness for more than one property has not been established. Valium is also the only benzodiazepine providing *diazepam*—pharmacologically active itself—as well as the other active metabolites desmethyldiazepam, 3-hydroxydiazepam and oxazepam. Though it can not be related specifically to clinical effects, this aspect of the pharmacokinetic profile of Valium also sets it apart from other benzodiazepines.



The unique Valium (diazepam) structure.

Valium (diazepam) has a range of clinical applications no other benzodiazepine can match. Because of its three clinically proven pharmacologic properties, Valium is indicated in an impressively broad range of disorders. Adverse reactions more serious than drowsiness, fatigue or ataxia are rare. (See summary of product information.) Ambulatory patients taking Valium should be cautioned against driving, operating dangerous machinery, or the simultaneous ingestion of alcohol or CNS-depressant drugs. The following table gives more specific examples of a range of clinical applications unmatched by other benzodiazepines.

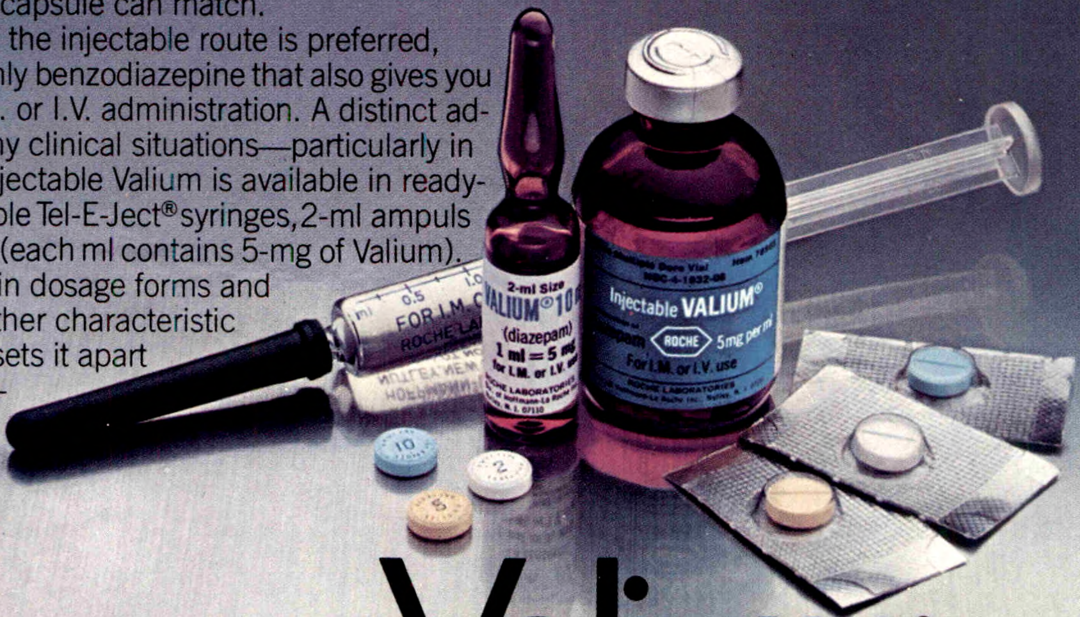
Indication:	Examples of Clinical Use:
Psychic Tension/Anxiety Symptomatic relief of tension and anxiety and certain psychoneurotic states	Administered orally, or injectably in acute cases, for symptomatic relief of tension and anxiety states resulting from stressful circumstances; whenever somatic complaints are associated with emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation.
Premedicant for Excessive Anxiety and Tension	Administered I.M. (preferred route) prior to surgery. Administered I.V. prior to cardioversion and adjunctively prior to endoscopic procedures.
Skeletal Muscle Spasm Adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of muscles or joints or secondary to trauma)	Administered orally or injectably in skeletal muscle spasm associated with low back syndrome, lumbar or lumbosacral sprain, cervical strain, fibrositis and osteoarthritis.
Spasticity Adjunct for the relief of spasticity caused by upper motor neuron disorders	Administered orally or injectably in skeletal muscle spasticity associated with hemiplegia, quadriplegia, paraplegia, cerebral palsy; athetosis; stiff-man syndrome. Administered injectably in tetanus.
Certain Convulsive Disorders	Administered I.V. adjunctively in status epilepticus and severe recurrent seizures.

does so much so well.

Valium (diazepam) offers unmatched flexibility in its various dosage forms and strengths. Oral Valium is available in a 2 mg strength for milder symptoms and for geriatric patients, 5 mg for moderate symptoms and 10 mg for the more severe. And because it's the only benzodiazepine tranquilizer supplied in *scored* tablets, Valium's dosage is the easiest to increase or decrease depending on a patient's individual and changing needs. That's dosage flexibility...dosage flexibility no tranquilizer capsule can match.

And when the injectable route is preferred, Valium is the only benzodiazepine that also gives you a choice of I.M. or I.V. administration. A distinct advantage in many clinical situations—particularly in the hospital. Injectable Valium is available in ready-to-use disposable Tel-E-Ject® syringes, 2-ml ampuls and 10-ml vials (each ml contains 5-mg of Valium).

Flexibility in dosage forms and strengths. Another characteristic of Valium that sets it apart from other benzodiazepines.



Valium®
(diazepam) Ⓘⓥ
One of a kind.

Please turn page for a summary of product information.

Valium®
(diazepam)

2-mg, 5-mg, 10-mg scored tablets
2-ml Tel-E-Ject® disposable syringes
2-ml ampuls
10-ml vials
5mg/ml

- **a distinct pharmacokinetic profile that includes diazepam and three active metabolites**
- **the *one* benzodiazepine with *three* clinically useful pharmacologic properties**
- **a range of clinical applications unmatched by any other benzodiazepine**
- **dosage flexibility no other benzodiazepine can match**

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome. *Oral form* may be used adjunctively in convulsive disorders, but not as sole therapy. *Injectable form* may also be used adjunctively in: status epilepticus; severe recurrent seizures; tetanus; anxiety, tension or acute stress reactions prior to endoscopic and surgical procedures; cardioversion.

Contraindications: Use of Injectable in infants and Tablets in children under 6 months of age; known hypersensitivity to drug; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: As with most CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Advise patients against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals (drug addicts or alcoholics) under careful surveillance because of their predisposition to habituation and dependence. Use of any drug in pregnancy, nursing women or in women of childbearing potential requires that expected benefit be weighed against possible hazard.

ORAL: Not of value in treatment of psychotic patients; should not be employed in lieu of appropriate treatment. When using oral form adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may also be associated with temporary increase in frequency and/or severity of seizures.

INJECTABLE: *When used I.V., the following procedures should be undertaken to reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment. Inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; extreme care should be taken to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Administer with extreme care to elderly or very ill and those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; resuscitative facilities should be available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓ and administer in small increments. Not recommended for OB use until additional information is available. Should not be administered to patients in shock, coma or in acute alcoholic intoxication with depression of vital signs.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Limit oral dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed or tolerated).

INJECTABLE: Laryngospasm and increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic and have necessary countermeasures available; hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly and debilitated; safety and efficacy in children under 12 not established.

Adverse Reactions: Side effects most commonly reported were drowsiness, fatigue and ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued.

Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Valium (diazepam) therapy and are of no known significance.

INJECTABLE: Venous thrombosis and phlebitis at injection site, hypoactivity, syncope, bradycardia, cardiovascular collapse, nystagmus, urticaria, hiccups, neutropenia.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat or chest have been reported.

Dosage: Individualized for maximum beneficial effect.

ORAL–*Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg *b.i.d.* to *q.i.d.*; acute alcohol withdrawal, 10 mg *t.i.d.* or *q.i.d.* in first 24 hours, then 5 mg *t.i.d.* or *q.i.d.* as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg *t.i.d.* or *q.i.d.*; adjunctively in convulsive disorders, 2 to 10 mg *b.i.d.* to *q.i.d. Geriatric or debilitated patients:* 2 to 2½ mg 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg *t.i.d.* or *q.i.d.* initially, increasing as needed and tolerated (not for use under 6 months).

INJECTABLE: Usual initial adult dose is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., *dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Moderate psychoneurotic reactions, 2 to 5 mg I.M. or I.V. and severe psychoneurotic reactions, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary; muscle spasm, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); status epilepticus, severe recurrent convulsive seizures, 5 to 10 mg I.M. or I.V. initially, repeat in 2 to 4 hours if necessary. In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V., within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma and diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Immediate gastric lavage indicated for overdosage with tablets. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

Supplied: Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® (unit dose) packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10. Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam, compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

ROCHE
Roche Laboratories
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Nutley, New Jersey 07110

Malignant Melanoma in the American Black

EDWARD T. KREMENTZ, M.D.,* CARL M. SUTHERLAND, M.D.,† R. DAVILENE CARTER, M.D.,‡ ROBERT F. RYAN, M.D.§

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Tulane University School of Medicine,
1430 Tulane Avenue, and
Charity Hospital of Louisiana at New Orleans,
New Orleans, Louisiana

Malignant melanoma in the American Black is an uncommon disease. Scattered reports have appeared in the literature indicating a somewhat different behavior and distribution from melanoma in the White patient. The last published report prior to the organization of the Tumor Registry at Charity Hospital of Louisiana on melanoma in the Black was in 1948 by Muelling when 28 cases were reported. From 1948 through 1974, 96 additional patients have been recorded in the Charity Hospital Registry which represents the largest reported experience in the American literature. The average age at diagnosis is 57.8 years as opposed to 53 years for White patients observed over the same time period. The ratio by sex is essentially equal in Blacks. The disease usually presents on the palmar or plantar surfaces of the hands or feet in the Black. In the registry data 51% occurred on the lower limb, 11% on the upper limb, 6% on the trunk, 6% on the genitalia, 1% on the head or neck, 13% were of extradermal origin, and 10% had unknown primary sites. The 5-year cumulative survival for all Black patients in this series is 27%. In contrast to the poor overall survival, a 78% 5-year survival has been achieved in Stage I patients treated with perfusion, wide excision, and regional lymph node dissection.

MALIGNANT MELANOMA in the American Negro has been thought to be an extremely rare disease, a concept dating back to the authoratative paper by Rudolph Matas[15] in 1896 on "The Surgical Peculiarities of the Negro." Matas observed the rarity of melanoma in Blacks other than in the eye. He reported 3 White patients but no Blacks with melanoma treated at Charity Hospital of Louisiana at New Orleans. The next report concerning the Charity Hospital experience appeared in 1923 in a paper by Sutton and Mallia,[25] who cited the experience from Charity Hospital reported to them by letter from H. E. Menage who described 5 Black patients with melanoma treated at Charity Hospital, all of whom died of disease. The next reports from Charity Hospital were by Muelling[19] in 1948, and Muelling and Burdette[20] in 1950. Muelling reported 92 patients with melanoma seen from 1937–1947 with 28 occurring in Blacks and 64 in Whites. The preponderence of melanotic lesions occurring on the foot of Blacks was noted, as was the poor prognosis for the disease in both races, with the mean duration of survival being one and a half years in Blacks as compared to 4 years and 10 months in Whites.

The Tumor Registry at Charity Hospital was organized in 1953, and all cases of malignancy have been registered for analysis and followup from 1948 through the present time. Through 1974 there have been 576 patients with melanoma recorded in the registry, of which 96 occurred in Blacks. This report will be concerned with the characteristics of melanoma in Blacks as seen at Charity Hospital as well as survival according to the stage of disease, site and treatment.

Review of Literature

Malignant melanoma in the American Black was first described by Gilchrist,[7] in 1899 from Johns Hopkins University, who reported a 58-year-old Black male with metastatic malignant melanoma from a lesion on the sole of the foot. On reviewing the literature, he could only find reference to two previous cases in Blacks, neither of which included microscopic examination. In 1920

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* Professor of Surgery, Tulane University School of Medicine.

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‡ Assistant Professor of Surgery, Tulane University School of Medicine.

§ Professor and Chief, Section of Plastic Surgery; Acting Chairman, Department of Surgery, Tulane University School of Medicine.

This work has been supported in part by U.S. Public Health Service Grant Nos. CA05108 and CA05837, by the Eustis Fund for Cancer Research, and by the Marjorie Schwab Research Fund.

TABLE 1. *Distribution of Total Admissions and Tumor Registry Cases: Charity Hospital of Louisiana at New Orleans (1948–1974)*

Group	Total Admissions	Cases in Tumor Registry	Total (%)	Melanoma Cases	Registry Cases (%)
Black Female	752,631	12,805	1.7	52	0.4
Black Male	406,569	10,488	2.5	44	0.4
White Female	224,854	8,779	3.9	247*	2.8
White Male	211,675	11,789	5.5	233*	1.9
Total	1,595,729	43,861	2.75	576	1.3

* Verification pending for 1974 registry figures.

Hazen[10] reported a 44-year-old Black male with a primary of the foot and metastases. Sutton and Mallia[25] in 1923 described a malignant melanoma of the left foot with generalized metastases in a 78-year-old Black. In 1927, Des Ligneris,[5] reporting from the Elim Hospital in Northern Transvaal, reported 17 cases of melanoma. With the exception of one ocular case, all were located on the leg or foot. He postulated that the disease in Blacks was less malignant than in Whites. He cited one interesting case of spontaneous remission of metastatic disease following amputation of the "worst leg," and theorized that immunological mechanisms could reject the remaining tumor after the bulk of the disease had been resected. Bishop[4] in 1923 reported 9 additional cases of malignant melanoma occurring in American Blacks. This report included one patient with melanoma arising in the eye and one on the lip, and quotes an additional ocular case by Lister. He cited two additional cases reported to him by Bauer and three by Pack, one of which was located in the mouth, the first reported case in that site. He felt that there was an apparent influence of trauma associated with the development of melanoma. In 1939 Baxter[3] reported a second case of malignant melanoma in the mouth of a Black. In his review of the world's literature, he found references to an additional 224 cases of malignant melanoma of all sites in Blacks. The majority of lesions in Blacks were found on the foot (65.3%); 9.4% were in the eye, and the rest were at various other skin sites with two other extradermal lesions. He assumed that trauma to the feet was of importance in the etiology, although noting that the neoplasm frequently occurred in areas of change from heavy to light pigmentation. From this review, Baxter felt that the disease was more malignant in American than in African Blacks. Pack and Adair[22] reviewed the literature in 1939, and excluding African natives, found reports of 34 cases occurring in American Blacks, and added 7 cases from Memorial Hospital. In 1940 Anderson[1] reported 10 cases from the John Gasten Hospital in Memphis. His analysis revealed no morphological difference between malignant melanoma arising in Negroes and in Caucasians. Imler and Underwood,[11] in 1947, collected 73 cases of malignant melanoma in American Blacks in an extensive review of the literature. They added 6 cases including one of the nose, one in the mouth, and the first instance of a primary lesion in the anorectal area, from their own experience. In 1951 Morris and Horn[18] collected 280 cases reported in African Blacks and 158 in American Blacks, to which they added 9 additional cases from the Hospital of the University of Pennsylvania. They concluded that the neoplasm is not as rare as had been thought and occurred in a ratio range of from 4.4–1.8 Whites to one Black as reported in 4 different institutions. They noted the high frequency of foot lesions occurring irrespective of wearing shoes.

White *et al.*[27] in 1961 reported the experience of the Freedman's Hospital of 31 skin cancers of which only two were malignant melanomas. They concluded that skin cancer was not rare in Black patients, and exceeds the incidence of renal, testicular, thyroid and other endocrine cancers.

In 1963 Pack and Davis[23] reported 27 cases from the Memorial Hospital and the Harlem Hospital in New York City. They concluded that the tumor was not a rarity, and occurred at a White to Black ratio of approximately 4:1. They emphasized the high malignancy of these tumors with metastatic potential paralleling that of Caucasians. They confirmed the high incidence of tumor occurring on the feet. Since these patients were accustomed to wearing shoes, they felt trauma was not an etiologic factor.

Lewis[13,14] performed an extensive study of pigmentation and malignant melanoma. He established a relationship between pigmented lesions on the soles of the feet in African Blacks and the occurrence of malignant melanoma. He postulated "a high incidence of potentially unstable collections of melanocytes seen in the area, and that this is genetically determined."

In 1971 Shaw and Goldsmith[26] again reviewed the Memorial Hospital experience, and found 18 cases in Blacks. Some of these cases may be included in Pack's report. Due to the high percentage of foot lesions, they urged biopsy of any clinically suspicious pigmented lesion occurring on the foot.

Hambrick et al.[9] in 1974 reviewed the experience of the West Tennessee Cancer Clinic of skin cancer in

Blacks. They found 13 cases of malignant melanoma, and emphasized the aggressive tendency of this disease. Eleven of the 13 patients died of metastases, and one remained alive with metastases. They noted there was no large series of malignant melanoma in Blacks with long-term survival results.

In 1975 Giraud[3] reported on 380 cases of malignant melanoma in Blacks in South Africa. He found that the patients were generally older than Whites with this disease, that there was a slight preponderance of females, and that the majority of the lesions occurred on the foot. He was able to obtain long-term results in 79% of 100 patients seen at the Baragwanath Hospital, and found a 19.6% 5-year survival.

Material

Incidence According to Hospital Admissions

There have been 1,595,729 patients admitted to Charity Hospital of Louisiana at New Orleans in the 26-year period from 1948–1974. The distribution of the total patient population is shown in Table 1. The ratio of Black to White patients is approximately 2.5:1 with females accounting for 65% of Black admissions. This disproportion can partially be explained by the large number of obstetric admissions to this facility (32,093 Whites and 255,027 Blacks). The Charity Hospital Tumor Registry includes 43,861 cases, which represents 2.8% of the total number of hospital admissions. Distribution of cancer cases by race is nearly equal, with 53% being Blacks and 47% being Whites, which tends to indicate a proportionally higher incidence in Whites in view of the admission ratio. This may be an erroneous observation, due to age differences in the patient population by race at Charity Hospital, i.e., there are more younger Black patients. Malignant melanoma accounts for 1.3% of the total number of cases in the registry. Melanoma occurred in Blacks in only 96 (0.4%) of the registered cases while it accounts for 480 (2.3%) of the cases in Whites. The proportion of melanoma cases in Negro men and women is equal, while in Whites it is slightly higher for women than men (1.3:1). It is notable that only 6 Black patients with melanoma have been treated by the Tulane Surgical Service outside the Charity Hospital facility, compared to more than a thousand Whites treated in the past 15 years. The distribution of Black melanoma patients by service was as follows: 54 admitted to the Tulane Service, 36 to the L.S.U. Service, and 4 to the now discontinued Independent Service.

Site of Primary Lesions

The location of the primary melanoma is detailed in Fig. 1 and Table 2. There were 10 undetermined lesions, and these were arbitrarily placed with melanomas of dermal origin. The greatest number of lesions occurred

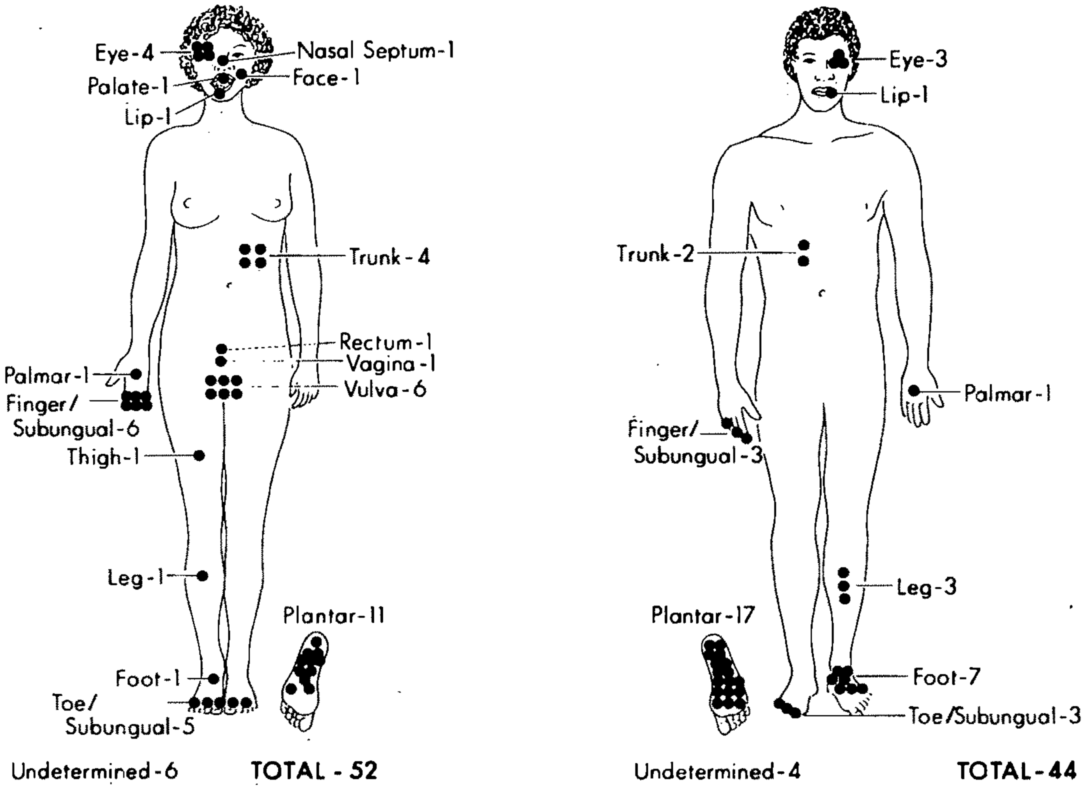

FIG. 1. Anatomic distribution of primary lesions in 96 Black patients according to sex.

TABLE 2. *Distribution of Cases by Primary Site*

Site	No. Pts.	Male	Female
Dermal			
Lower Extremity	49	30	19
Plantar	28	17	11
Toe/Subungual	8	3	5
Foot	8	7	1
Leg	4	3	1
Thigh	1	—	1
Upper Extremity	11	4	7
Palmar	2	1	1
Finger/Subungual	9	3	6
Trunk	6	2	4
Vulva	6	—	6
Face	1	—	1
Undetermined	10	4	6
Extradermal			
Eye	7	3	4
Gingiva	2	1	1
Palate	1	—	1
Nasal Septum	1	—	1
Rectum	1	—	1
Vagina	1	—	1
	—	—	—
Total	96	44	52

on the lower extremity. Forty-nine patients (51% of all lesions) had melanomas on the lower limbs and 11 had primary lesions on the upper limbs. Thirty-one per cent of all cases occurred on the plantar or palmar surfaces of the limbs, with 28 cases occurring on the plantar surface of the feet and two cases on the palmar surface of the hands. There were 13 extradermal melanomas, 7 occurring in the eye, one in the vagina, one in the rectum, and 4 in the oro- or nasopharynx, of which 2 occurred on the lip, and one each in the palate and nasal septum. Six lesions occurred on the vulva. It is not clear from the chart whether these were located in the labia majora or labia minora. Presumably those occurring on the labia majora would be of dermal origin and those on the labia minora would be of mucous membrane origin. Therefore, the vulvar lesions were arbitrarily included with the dermal lesions. There were 7 lesions occurring in the eye; 3 arose in the iris or ciliary body, 3 arose from the choroid (one of which extended into the optic nerve and sclera), and one was said to arise in the cornea and retrobulbar area but may have actually arisen from the mucous membrane of the orbit.

Age and Sex

Fifty-two of the patients were female and 44 were male (Fig. 2). The average age at diagnosis was 57.8 years. The age range of these patients is seen in Table 3. The range in males was from 4 months to 80 years with a median age of 56.9 years. The 4-month-old patient had a melanoma of the iris. The range for female patients was from 19–92 years with a median age of 58.6. The patients with dermal primaries had a somewhat higher median age of 59.6 years compared to 46.7 for the extradermal primaries. The most common lesion was seen in the foot and the median age for this group was 62.6 years, somewhat older than the median for all the patients.

Stage

Stage of disease is detailed in Table 4 and is separated according to localized disease (Stage I) including satellites within 3 cm of the primary. Regional disease (Stage II) includes those patients with cutaneous, subcutaneous, or lymph node metastases no further away from the primary than the first regional lymph node drainage basin. In the lower limbs this includes the femoral nodes and in the upper limbs the axillary nodes. Distant metastases (Stage III) includes patients with hematogenous spread or with other metastases beyond the first regional node draining area, including the iliac nodes for lower extremity lesions.

There were 37 patients with localized disease, 37 with regional disease and 19 with distant disease, and three with unknown stage. Six of the 7 eye patients presented with localized disease and 5 of the 6 vulva lesions presented with Stage II disease.

Type of Treatment

The type of treatment according to stage of disease is shown in Table 5. Excision of the primary consists of wide excision, usually a margin of 5 cm of normal tissue surrounding the tumor where possible, minor amputations for finger, toe and subungual lesions in 12 cases, and 5 major amputations were performed for

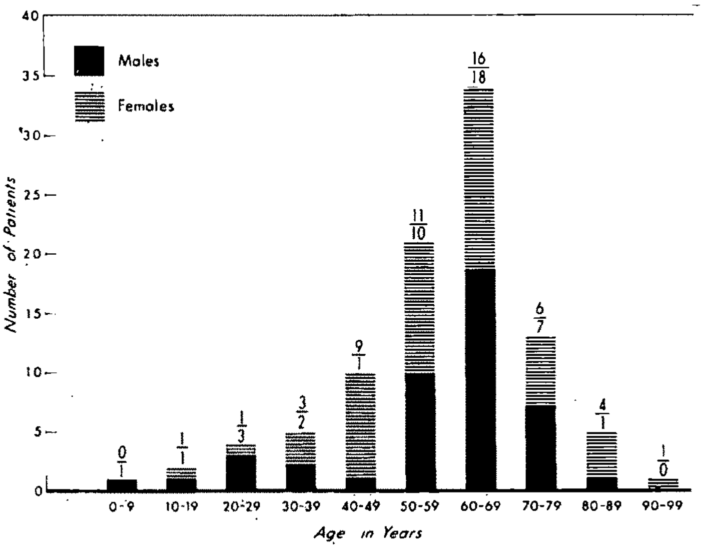

FIG. 2. Distribution of cases by decade according to sex and age at diagnosis in 96 Blacks with melanoma.

TABLE 3. *Age at Diagnosis in 96 Patients*

Group	Age Range	Median Age (yrs)
Males	4 mo–80 yr	56.9
Females	19–92 yr	58.6
Dermal Primary	16–92 yr	59.6
Extra-Dermal Primary	4 mo–70 yr	46.7
Primary on Foot	34–92 yr	62.6
Primary Eye	4 mo–70 yr	42.3
Overall Average	4 mo–92 yr	57.8

TABLE 4. *Stage of Disease at Diagnosis in 96 Patients*

Stage	Skin	Extradermal	Total
Local (I)			37
Male	12	3	
Female	19	3	
Regional (II)			37
Male	16	1	
Female	15	5	
Distant (III)			19
Male	11	0	
Female	7	1	
Undetermined			3
Male	1	0	
Female	2	0	
Total	83	13	96

melanoma of the extremity. The one major amputation on the Tulane Service was performed prior to the development of regional perfusion, and 4 were performed by the L.S.U. Service in the last 10 years. Three of the 4 patients who had amputations more than five years ago have died of disease, all of them having multiple node involvement. The one survivor had a single positive node. There were 5 patients who had excision of the metastatic tumor; 17 had excision and regional lymph node dissection including three patients who had Stage III disease.

One patient was treated by perfusion alone. This occurred in a 76-year-old woman who had a 5 cm lesion on the thenar eminence of the left palm in 1960. The patient refused amputation but accepted biopsy and chemotherapy by regional perfusion. This patient was perfused with 50 mg of Melphalan and 30 mg of Thio-TEPA® through the axillary artery. The lesion gradually regressed and the patient was disease free at last contact, one year ago. This patient was treated early in the series and received a dose of drug exceeding that currently recommended. She sustained forearm muscle damage, but has had the use of a partially functioning limb. Four patients with Stage II disease were treated by chemotherapy by perfusion and regional lymph node dissection, wide excision having been previously performed. Four patients were treated by perfusion and wide excision with Stage I disease. Seventeen patients had perfusion, wide excision, or minor amputation and regional lymph node dissection. Seventeen patients received no treatment, inadequate local excision, or refused treatment; 3 patients had chemotherapy without surgery.

Results

The survival by stage of treatment in the 96 patients is shown in Fig. 3. These curves show the cumulative per cent survival based on the method described by Cutler and Ederer. The overall survival for all patients at 5 years was 27% and 21% at 10 years. In Stage I the salvage was 71% at 5 years and 56% at 10 years. In Stage II the salvage dropped to 17% at 5 years and 13% at 10 years. In Stage III, which included three patients with undetermined stage, the survival was 9% at two years and all had succumbed by the third year. When the results are reviewed for the dermal melanomas (Fig. 4), the Stage I survival at 10 years is 44%, slightly lower than the overall Stage I group. Salvage in Stage II at 10 years was 17% which is slightly higher than the overall salvage, and in Stage III all patients were dead by the third year. In the extradermal group (Fig. 5), the salvage for Stage I at 10 years was 54%, which included 6 eye patients. The remaining salvage was poor in Stage II disease, 17% for 6 patients at 5 years, with all being dead by the sixth year. One patient in Stage III survived one year. When the 5-year survival is examined by specific sites for all stages (Fig. 6), the 7 eye patients had a salvage of 67%. For upper limb lesions, the 11 patients had a 53% salvage rate; the 6 trunk lesions had a salvage rate of 50%; the 49 patients with lower limb lesions had a survival of 22% and 6 vulvar lesion patients were dead within 2 years. Seventeen patients were excluded from this table as 10 had undetermined primary lesions and the remainder consisted of one to two patients per site.

Chemotherapy by regional perfusion was introduced at Tulane in 1957 and has been particularly useful in the treatment of melanoma of the extremities.[12] In this series 26 patients have been treated by regional perfusion,

TABLE 5. *Modes of Therapy in 78 Patients With Melanoma of the Skin With No Prior Definitive Therapy*

Treatment	Stage I	Stage II	Stage III	Undetermined
Excision of Tumor	8	3	3	1
Excision & RLND	4	12	1	—
Regional Perfusion	1	—	—	—
Perfusion & Excision	4	—	—	—
Perfusion & RLND	—	4	—	—
Perfusion, Excision & RLND	5	10	2	—
Exploratory Surgery*	—	—	2	—
Chemotherapy	—	—	2	—
Inadequate or No Therapy	5	1	8	2

* One patient with Stage III disease had subsequent chemotherapy.
Note: Excision included 15 minor and 5 major amputations.

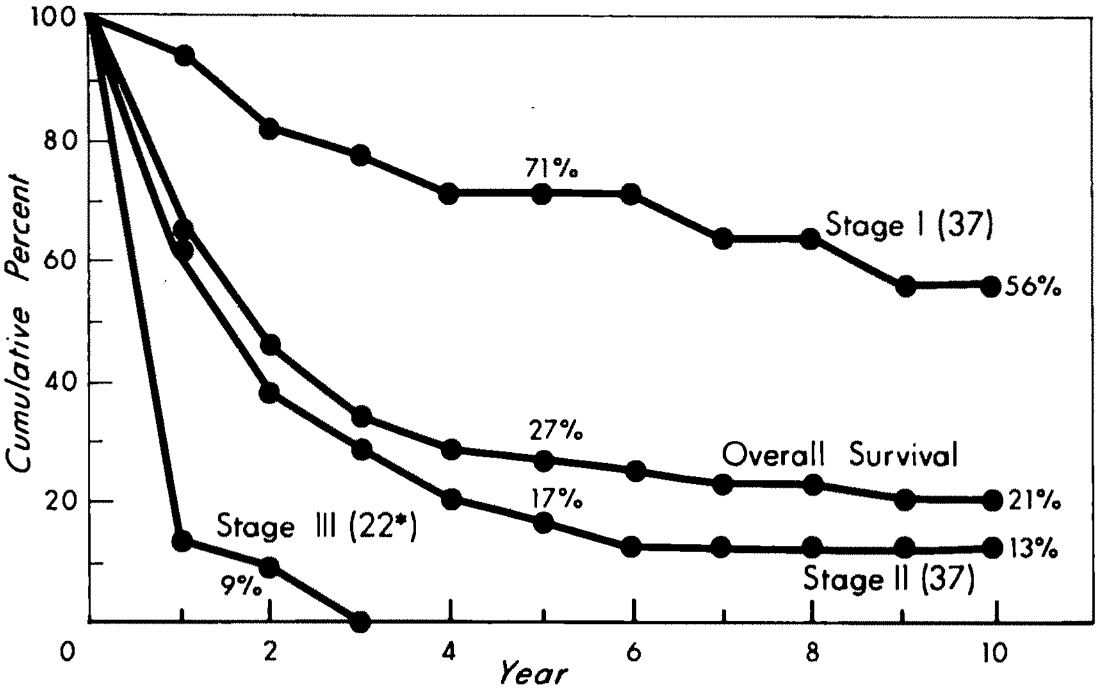

FIG. 3. Cumulative survival curves for 96 Black patients by stage of disease at diagnosis. (*) Includes undetermined Stage three patients.

25 of whom had additional excisional surgery. There were 10 Stage I patients treated by perfusion, 9 of whom had excisional surgery. The 5-year cumulative salvage in this group was 78%. There were seven patients with Stage I melanoma of the foot who were treated by wide excision; two had regional lymph node dissection in addition. The 10-year survival was 23% for this group. There were an additional 8 patients who had perfusion and wide excision, 4 of whom had regional lymph node dissection. The 10-year survival for the latter group was 57% (Fig. 7), a significant improvement compared to the nonperfused group at the 95% confidence level. For comparison, the results obtained in 38 Whites with Stage I melanoma of the foot treated by regional perfusion and wide excision is also included in Fig. 7. Twenty-nine of these patients had regional lymph node dissection in addition to wide excision. The survival at 10 years was 48% for this group, which was not significantly different from the similarly treated Black group.

Discussion

There have been conflicting reports and opinions on the aggressiveness of malignant melanoma in Blacks. This is the first report of a large series of patients with a 100% followup. The overall cumulative survival rate is 21% at 10 years and confirms the aggressiveness of this disease. However, a cumulative 10-year survival rate of

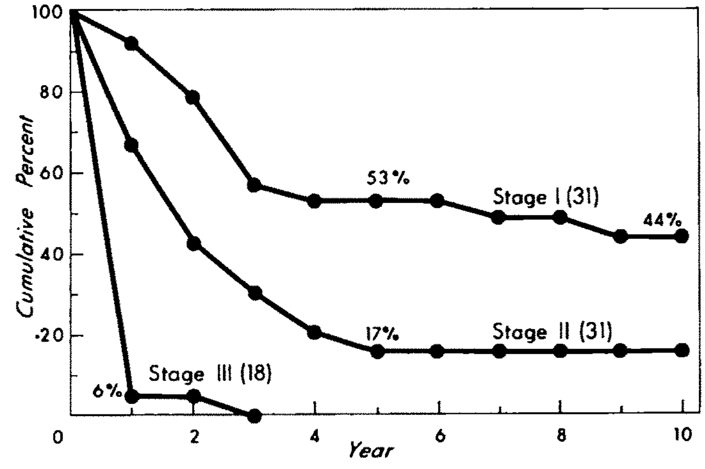

FIG. 4. Cumulative survival curves for 80 Black patients with dermal melanoma by stage of disease at diagnosis.

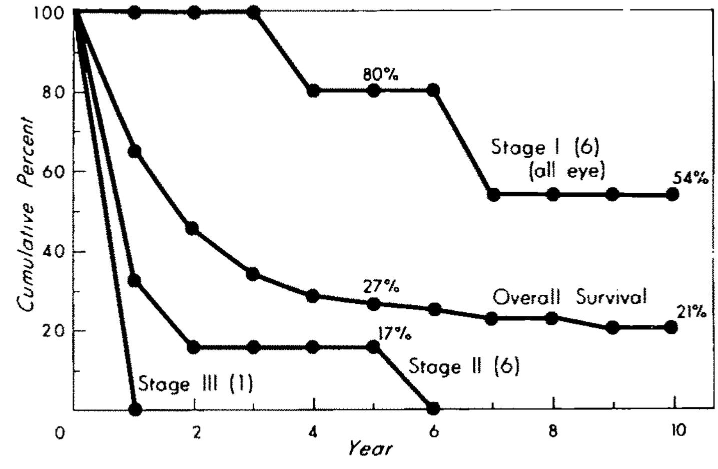

FIG. 5. Cumulative survival curves for 13 Black patients with extra-dermal melanoma by stage of disease at diagnosis.

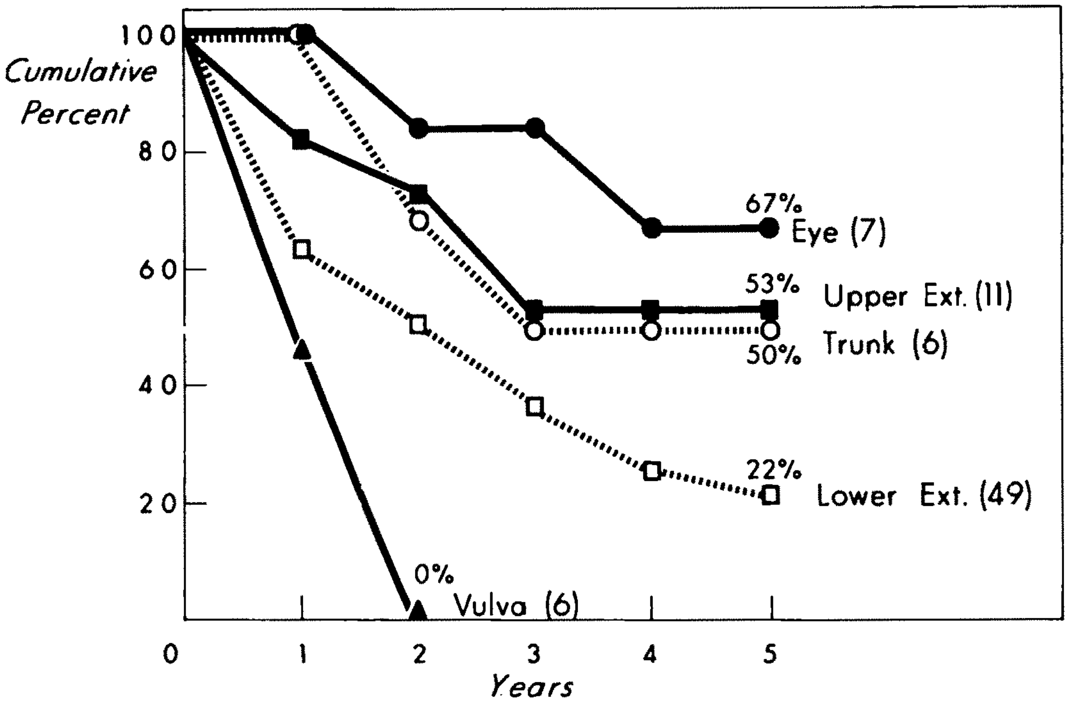

FIG. 6. Cumulative survival curves by site of primary in 79 Black patients with all stages of melanoma. Excluded: 10 patients with undetermined primary sites and 7 patients with miscellaneous sites (gingiva 2; vagina, palate, rectum, skin of face, and nasal septum, one each).

44% in Stage I patients with dermal melanoma compares favorably with that obtained in White patients.[12,13,16] It would appear that aggressive surgical therapy in early lesions without regional metastasis will give a favorable outcome in Blacks as well as Caucasian patients.

This study continues to confirm the difference in site distribution of melanomas in the Black as compared to Whites and the similarity of distribution to that found in the African Black and in the Hindu.[3] As is noted in Table 1, 28 lesions occurred on the plantar surface, 8 in the toe and subungual area of the foot, and 11 in the palmar/finger/subungual area of the hand. All of these sites are the lightly pigmented portions of the skin. If the "Undetermined" and "Extradermal" sites are excluded (23 patients), 64% (47/73) of all lesions appeared in

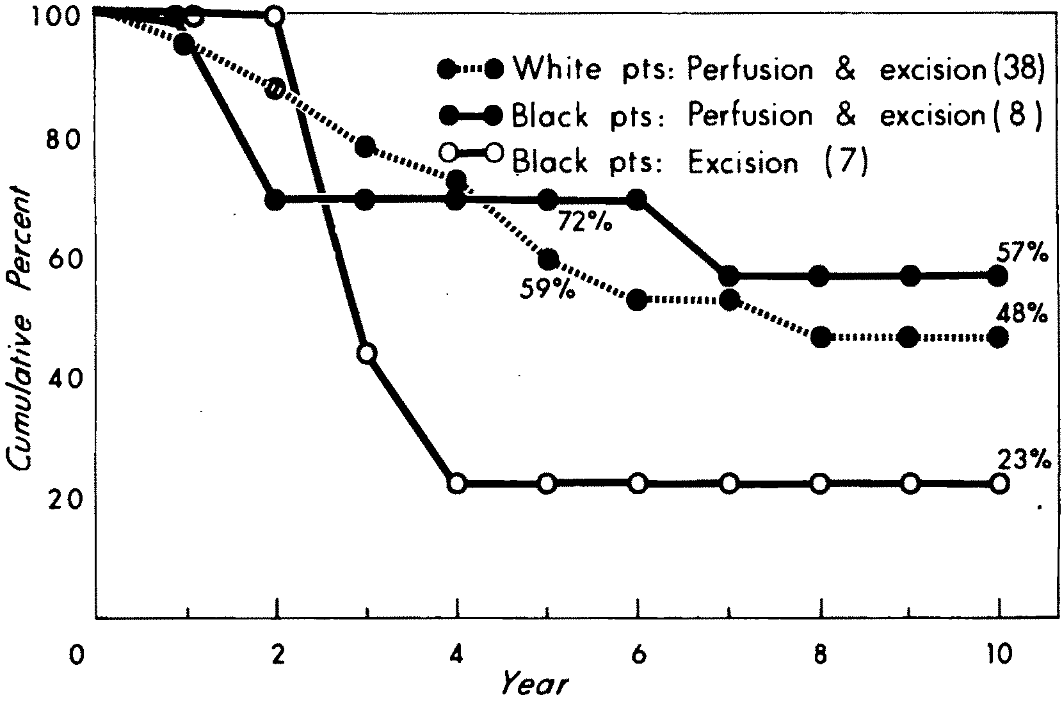

FIG. 7. Comparison of cumulative survival curves by type of treatment in 15 Black and 38 White patients with Stage I melanoma of the foot.

the most lightly pigmented portion of the skin, a finding noted by others.[16] Almost all of our patients normally wear shoes, so we can not implicate foot trauma as an etiological factor. It would seem that the evidence and theories presented by Lewis[13,14] regarding unstable pigmented spots on the foot best explains the high incidence of melanoma on the feet of Negroes.

The relative frequency of eye lesions in the Black previously noted by others[3,15] occurred in this group. However, the prognosis in this group was better than in all other sites. The common occurrence of melanoma in the mucous membrane in Blacks was also noted, particularly in the female. The high incidence of vulvar lesions was again seen in this series.

The pathological characterization of melanoma in the Black is somewhat different than is seen in Whites. The occurrence of lentigo maligna commonly seen on the sun exposed skin of the elderly White patient is rarely, if ever, seen in the Black. The lesions occurring on the palmar and plantar surfaces are difficult to classify and consist of nodular invasive melanoma or melanomas with radial growth components.[17]

The latter lesions show marked variation in color from brown to blue to black; the surface and borders are irregular with papillary growths, nodules and hyperkeratoses. These latter lesions have been the subject of a special study by Arrington and Reed[2] of the Department of Pathology at Tulane University. They have collected 27 cases, primarily from Charity Hospital, which have been characterized as acral lentiginous melanoma (ALM). This is the fourth variant to the three generally recognized pathological variants, i.e., lentigo maligna, superficial spreading melanoma, and nodular invasive melanoma, as described independently by Clark[17] and McGovern.[16] ALM is more commonly seen in the Black, as 18 of the 27 appeared in Black patients in their series. Histologically, ALM shows a diffuse melanocytic dysplasia and hyperplasia involving the basal portions of the epidermis with variation in epidermal hyperplasia. The melanocytes are usually spindle shaped but may be epitheloid, and possess heavily pigmented dendrites that extend into the hyperplastic epidermis. The papillary dermis on the palms and soles is usually inconspicious, which makes evaluation by level of skin invasion difficult and unreliable. However, in some areas, the papillary dermis may become markedly thickened and filled with tumor cells. Grossly, the tumor starts as a pigmented macule and extends radially with thickening in the central portion, in contrast to the superficial spreading melanoma in which polypoid nodules occur and there is regression of tumor in the center of the lesion. Eventually the ALM produces heavily pigmented plaque which thickens and ulcerates. Arrington and Reed have pointed out that these lesions have a poor prognosis with 18 of 27 patients dying of metastases (11 of them being Blacks). They also observed that patients with small lesions with lower levels of invasion had a reasonably good prognosis. Mucous membrane melanomas usually have a lentiginous radial component that is comparable to that of ALM. It has been noted that a possible reason for the prevalence of mucous membrane lesions in the Black is the association with areas of pigmentation occurring in the mucous membrane of the Black.[13]

There are no good data on the incidence of this disease in the American Black. As our Tumor Registry data are not area based, we can not accurately calculate the incidence of this disease. It is our impression that the incidence is between 0.5–1/100,000 Blacks per year.

Conclusions

From our review of the literature and from the Tumor Registry records of Charity Hospital, we feel that malignant melanoma in the American Black is an uncommon, but not rare, neoplasm. It was noted that a prominent difference exists between Blacks and Whites in regards to the site of origin of the tumors in that the melanoma in Blacks are relatively more common on plantar and palmer surfaces of the feet and hands, toes, fingers, and mucous membranes. We have found melanoma to advance rapidly in the Black with bad prognosis in the advanced stages. Aggressive surgical therapy consisting of wide excision of the primary lesion or minor amputation, and regional lymph node dissection in early stages produces long-term survivals. Regional chemotherapy by perfusion appears to improve the survival in extremity lesions.

Although some authors have felt that foot trauma might be a strong etiologic factor in malignant melanoma, we have found no evidence to support this theory.

Acknowledgments

The authors wish to express their appreciation to Ms. Jane Roberts, Executive Director of the Charity Hospital Tumor Registry, for supplying us with the statistical data from the Tumor Registry records, to Mrs. Marilyn Campbell, R.N., for compiling the data for the tables and figures, and to Ms. Elizabeth Ewing for medical illustrations. The authors also wish to thank the numerous other persons who provided assistance on this project.

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DISCUSSION

DR. LASALLE D. LEFFALL, JR. (Washington, D.C.): I had the opportunity to review the manuscript of the paper that was presented by Dr. Krementz, and I would like to congratulate him and his colleagues on their presentation, primarily for keeping this topic before the surgical community, and to state what can be done when the disease is caught in the earlier stages. And as you will note in his presentation, he stated that in the Stage I disease the five-year survival was roughly comparable in black and white patients.

The information that he presented is really what we have noted at the Howard University Hospital and the D. C. General Hospital on our service there, as far as the location of the lesions is concerned and the types of lesions which one has, which was gone into in more detail in his paper. However, I must say that the numbers we have are much smaller than he has presented in his series. He does have the largest series reported.

It's interesting that when I visited Nigeria some three years ago, and made rounds at their big teaching hospital, which is the University of Ibadan, in Nigeria, I saw three patients on rounds who had malignant melanoma. All of them had it on the feet, the plantar aspect, and two of the three had huge nodes in the groin. A third patient had smaller but clinically positive nodes in the groin also. It seems as though the disease was found at a much later stage in its development. Therefore, these patients came in much later.

It's interesting that my colleagues in Africa still don't know what role trauma plays. They were trying to say that trauma plus the heat played some role, but there were many patients whom they see who are barefooted and who were walking around in the heat, so, therefore, the role of trauma still is not clear.

Some of you may recall a report that came from Howard University which was substantiated by the National Institutes of Health, talking about the increased cancer mortality in blacks. Some people have questioned that, and were wondering if these data were really what they were purported to be. I had a conversation recently with Dr. John Berg, of Iowa, where the black population is very small—perhaps less than 4 or 5%. He told me that he thought that he could show the same types of curves that we showed, based on socioeconomic status, and therefore the stage of the disease that the patient has when that patient presents himself or herself to the doctor.

We are studying this further at our institution, and I'm sure that the data that Dr. Berg spoke to me about will be presented in greater detail. As I said, it was interesting that when we had comparable stages of the disease, the five-year survival was essentially the same in black and white patients.

DR. HERBERT B. WREN (Texarkana, Arkansas-Texas): I was a resident at the time that many of these patients were seen at Charity Hospital. I reminded Dr. Krementz when I read the manuscript of the paper that one of the patients in his series had a melanoma of the toe. This was one of the patients that had wide excision and perfusion. It wasn't known at the time, but the patient was pregnant when she was perfused. She subsequently delivered a normal baby. Dr. Krementz tells me that there have been two other patients who were pregnant at the time they were perfused.

I rise to ask if there are any other doctors here who have had this experience in perfusion of patients who are pregnant at the time of perfusion.

DR. C. M. SUTHERLAND (Closing discussion): In response to Dr. Wren's question, we don't necessarily recommend perfusion in the pregnant female, but the isolation must have been fairly good in these particular cases, because there have been no problems to date with these particular females.

I'd like to take a moment with Dr. Leffall's point on foot trauma as a possible etiologic agent in malignant melanoma in the Negro. Most of the reported cases of malignant melanoma in the Negro are from the African literature, and have been in the African native. It has been theorized, as he pointed out, that the high incidence of lesions in the foot is related to the foot trauma in these people from going barefoot. Our series parallels the African literature as to the site, and our patients do not go barefoot, which does not support this theory.

Also, there were some interesting data presented from the work that Martin Lewis did in the sixties when he was in Uganda. He did an extensive study on pigmentation of the feet in Ugandan natives, and established a relationship between pigmented lesions of the foot and the occurrence of malignant melanoma in the African Negro. He postulated at that time a high incidence of potentially unstable melanocytes in the feet, and that this is genetically determined. We have not been able to analyze our Negro series as to genetic predisposition of malignant melanoma, but have found a significant incidence of this in our Caucasian patients. It may be that malignant melanoma in both Negroes and Caucasians occurs because of genetic factors that are as yet incompletely understood.

In this particular spot, I can take a second, I think, to discuss Dr. Humphrey's presentation, which I enjoyed very much. I think it's very interesting data. We also use immunotherapy for Stage II and Stage III patients, as well as beginning to get into Stage I patients, as has been suggested, with a number of techniques. I won't take the time to discuss all of these, but I would like to comment on our experience with the use of autologous irradiated cells versus pooled cells.

Our experience has been quite similar to that reported earlier of Dr. Humphrey's, in that as far as clinical remissions, disease-free intervals, and immune parameters, we have been much more impressed with the use of autologous tumor cells, as opposed to some form of pooled-cell material for immunization.

Critical Analysis of Treatment of Stage II and Stage III Melanoma Patients With Immunotherapy

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Over the past 8 years, 244 patients with Stage II or III melanoma have been treated by cutaneous injection of a crude acellular homogenate of allogeneic melanoma cells (V-I) or a more concentrated fraction (V-II), followed in most patients by exchanges of WBC between paired partners. Patients with Stage III disease exhibited an overall response rate of 24% and prolongation of survival compared with control data. Stage II patients also had prolonged survival and reduced rate of recurrence over historic peers' data. Breakdown of subgroup data revealed that V-II plus exchange of WBC is similar to V-I plus exchange or V-II alone. However, recent experience with LTF suggests a higher response rate than in either V-I or V-II groups, particularly when autochthonous tumor is used for cross-immunization. The most meaningful immunologic data resulted from analysis of DNCB and MIF data. Patients negative to DNCB rarely respond to immunotherapy. A positive pretreatment MIF or positive conversion following treatment correlates with response, whereas, conversion of positive to negative predicts poor clinical performance.

SEVERAL CLINICAL TRIALS have demonstrated successful treatment of micro and macro metastases of melanoma using a variety of immunotherapeutic techniques. Morton et al. have recorded regression of approximately 90% of subcutaneous and cutaneous melanoma nodules directly injected with Bacillus Calmette Guerin (BCG).[11] In addition, several other noninjected nodules were noted to regress. Seigler also has shown, using a complex multiple treatment program of active specific and nonspecific immune stimulation, that melanoma-bearing hosts can be benefited by immune manipulation.[16]

Sumner and Foraker were the first to demonstrate that adoptive techniques can be effective.[20] One of two patients transfused with whole blood removed from another melanoma patient who had complete "spontaneous regression" also had complete disappearance of all tumor. Nadler and Moore cross-immunized paired patients with each other's tumors.[13] After the tumor implants were rejected or removed, patients' whole white blood cells (WBC) were cross-exchanged. One hundred thirteen patients with melanoma were treated in this fashion and 23 had objective tumor regression.[14] Krementz later confirmed this observation using a similar system.[9] Humphrey et al. demonstrated that an acellular tumor homogenate could be used instead of whole melanoma cells to immunize paired melanoma patients, thereby reducing the potential hazard of tumor inoculation.[6]

This report summarizes 8 years of experience with active and adoptive immunotherapeutic techniques used to treat patients with disseminated and recurrent melanoma, and most recently, used to treat patients with a high risk of developing recurrence after surgery for primary operable melanoma.

Materials and Methods

Over the past 8 years, 224 patients, 180 with Stage III (proven disseminated or recurrent disease) and 44 patients with Stage II (nodal metastases from primary disease of the torso or extremities present but no known disease following surgery) have been treated by active stimulation with allogeneic acellular melanoma preparation alone or in combination with exchange of WBC. Recently, 11 patients with Stage II or Stage III disease paired

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TABLE 1. *Sex and Primary Sites of 44 High-Risk Melanomas from KUMC Compared with 230 Patients from Ellis Fischel*

	Ellis Fischel	KUMC
Male/Female Ratio	1.15:1	1.59:1
Head and Neck	34*	9
Lower Extremity	29	23
Trunk	19	44
Upper Extremity	15	23

* Results expressed as per cent of total.

with patients with other types of malignancies have been treated by cross-immunization with radiated tumor cells followed by cross-transfusion of lymphocyte transfer factor (LTF) as described by Smith et al.[17]

The acellular homogenates used for immunization have been previously reported.[7] Briefly, the first preparation, Vaccine I (V-I), was prepared by finely mincing tumor and preparing a 20% W/V suspension of melanoma tissue removed surgically or at autopsy in phosphate buffer solution (PBS). The suspension was rendered acellular by rapid freezing and thawing. This homogenate was later refined by centrifuging three times at slower speeds and finally at 102,000 × g for 30 minutes. The final supernatant fraction, termed Vaccine II (V-II), was concentrated 10:1 by Diaflo vacuum filtration. Most patients receiving V-I were given 4 weekly injections of 1.0 ml, intracutaneously and subcutaneously, followed by 4 or 5 cross-transfusions of WBC and serum, equivalent to one pint of blood each. Patients treated with V-II received 8 weekly injections of 1.0 ml each, followed by booster injections at three-month intervals. Following immunization with V-II, patients either received no further treatment or were paired and cross-transfused with WBC alone from three pints of blood, or more recently WBC from 6 pints of blood prepared by leukophoresis on a Latham cell separator. The tumor equivalence† of V-I is 0.20 grams tumor per ml, and V-II is 2.0 grams tumor per ml.

Because it appeared that regression of tumor and increased survival could be produced by immunotherapy with no clinical evidence of harm, i.e., enhanced tumor growth, graft-versus-host reaction, anaphylaxis, etc., it seemed reasonable to study patients with no known disease but with a greater than 50% chance of developing recurrence. Forty-four patients have been entered in this study to date. Forty-two were treated with Vaccine II with or without WBC exchange, and two with LTF. The distribution of the primary site and sex of these patients is given in Table 1. All of the patients had either positive regional nodes or were judged to be high risk because of the primary site, i.e., anorectal or scalp.

The most recent study was undertaken to evaluate V-II plus WBC exchange versus LTF. All patients in this study were completely staged with scans, x-rays, and when necessary, surgery, into Stage II or Stage III groups. Previously prepared randomization cards were then used to select the type treatment for each patient. Patients in the LTF group were paired with nonmelanoma partners and were cross-immunized with each other's tumor or allogeneic tumor of identical histologic type if autochthonous tumor was not available. The immunizing dose used in the LTF group consisted of 20 mg of tumor, minced finely enough to pass through an 18-gauge needle. The tumor was treated with Cobalt-60 to 2500 R prior to injection. Patients received the minced radiated tumor at two-week intervals. After three injections, patients underwent leukophoresis of one pint of blood and the separated WBCs were used to prepare LTF by freezing and thawing 6 times followed by dialysis against distilled water and ultrafiltration to concentrate the volume to 1.0 ml. Following skin testing for hypersensitivity, 1.0 ml was given intramuscularly. The paired patients then were restimulated by tumor injection and donated and received 1.0 ml of LTF every two weeks for total doses ranging from two to 15, determined by partner availability.

All 224 patients were observed for clinical response and survival. Response was defined as 50% reduction in diameter of measurable tumor or clearly measurable regression less than 50%, which was sustained for at least three months and no new tumor development. Survival was measured by the life table method as described by Cutler and Ederer.[3]

All patients for the last 4 years have been evaluated for cutaneous delayed hypersensitivity reactions to dinitrochlorobenzene (DNCB) as described by Catalona.[2] All patients were sensitized by topical application of 2000 micrograms of DNCB in 0.1 ml of acetone. A spontaneous flare at the sensitization site at two weeks or a positive reaction to a challenge of 50 micrograms of DNCB at a separate site was interpreted as positive. In addition, patients were treated with four recall antigens: mumps (Lilly, 2 units), PPD (Parke Davis, 5 units), Monilia (Hollister-Stier, 1/100), and Trichophyton (Hollister-Stier, 1/20). Responses to intradermal injection of 0.1 ml of antigen exceeding 1.0 cm induration were considered positive.

Several in vitro tests have been used over the past 8 years. Serologic immunity evaluated by complement fixa-

TABLE 2. *Response Rate in Patients with Stage III Melanoma Treated by Active Immunization With and Without Exchange of WBC or LTF*

V-I plus Exchange	7/33*	21%
V-II only	8/40	20%
V-II plus Exchange	9/32	28%
LTF	3/9	33%
Total	27/114	24%

* Only data from patients with measurable disease are presented.

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† Weight of tumor required to produce 1 ml of vaccine.

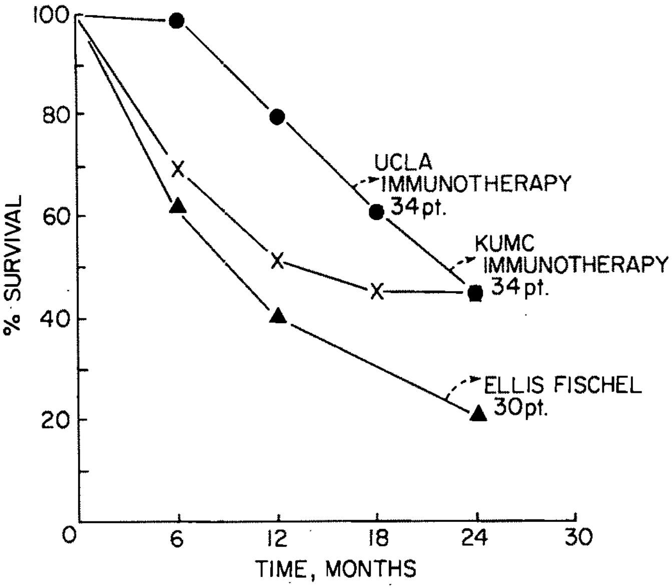

FIG. 1. Survival of Stage III melanoma patients treated at the University of Kansas Medical Center (KUMC) with immunotherapy without "debulking" surgery compared to patients treated at UCLA with Immunotherapy and Ellis Fischel control data.

tion, immunodiffusion, and by activity of sera against primary culture growth of identical but allogeneic tumor has been reported previously by Humphrey et al. and will not be reiterated here.[7]

Recently, patients have been evaluated by measuring total peripheral lymphocyte counts (TLC) and the per cent distribution of thymus-dependent (TDL) and bursa-dependent (BDL) lymphocytes. Sheep red blood cell (RBC) rosette formation as reported by Mendes was used for TDL assay and antibody-coated sheep RBC were used for BDL analysis.[12] Complement-dependent (EAC) and noncomplement-dependent (EA) fractions were also recorded. Lymphocyte sensitization was monitored with a migration inhibition factor (MIF) by a modification of the test described by Soborg and Bendixen.[18] Patients' peripheral leukocytes were placed in capillary tubes with and without allogeneic melanoma antigen (V-II preparation, see above). Inhibition of migration of leukocytes by 20% or more in the antigen-versus-nonantigen tubes was regarded as positive.

Results

Clinical response rates of measurable lesions in 114 patients with disseminated melanoma are shown in Table 2. Sixty-six patients with no measurable lesions are excluded from these data. All responses were noted in intradermal or subcutaneous disease except one patient with a 3 cm lesion of the frontal bone which disappeared while on LTF therapy. Several laboratory studies based on these patients have been previously reported, including the observation that in general, total peripheral lymphocyte counts increase in responding patients and decrease in patients with unrelenting progression.[15] The incidence of delayed cutaneous hypersensitivity reaction (DHR) at the site of vaccine injection increased from 10% with V-I to 62% with V-II.[7]

Responses were seen in all four treatment groups. Response to V-II plus exchange of WBC appears higher than V-I plus exchange or V-II only. However, the differences are too small to be significant with these sample sizes.

Survival data of 34 consecutive patients with Stage III disease, 24 treated with V-II plus exchange, 7 with vaccine II only and 3 with LTF are shown in Fig. 1. These data are compared to a similar group of patients treated with immunotherapy at UCLA by Morton et al.,[11] and Stage III patients from Ellis Fischel Hospital.[10] Unlike the UCLA group, none of these patients underwent surgery to "debulk" the tumor mass. It can be seen in Fig. 1 that survival at 24 months is equal to that reported by Morton and approximately twice the rate expected from the Ellis Fischel data. Analysis of data from the

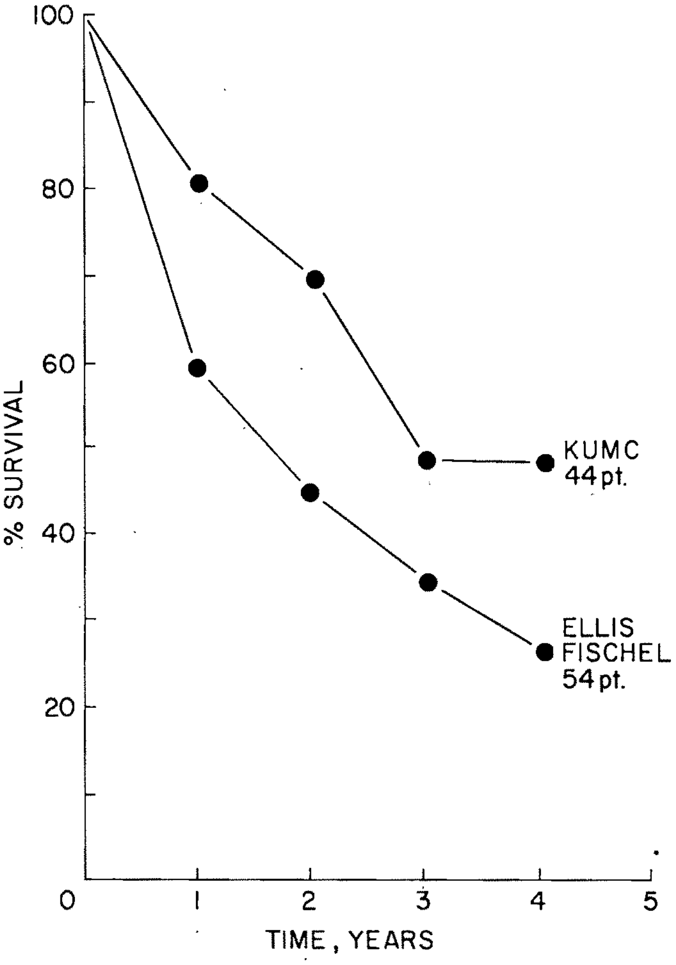

FIG. 2. Survival of high-risk melanoma patients from University of Kansas Medical Center (KUMC) compared to historic control data from Ellis Fischel.

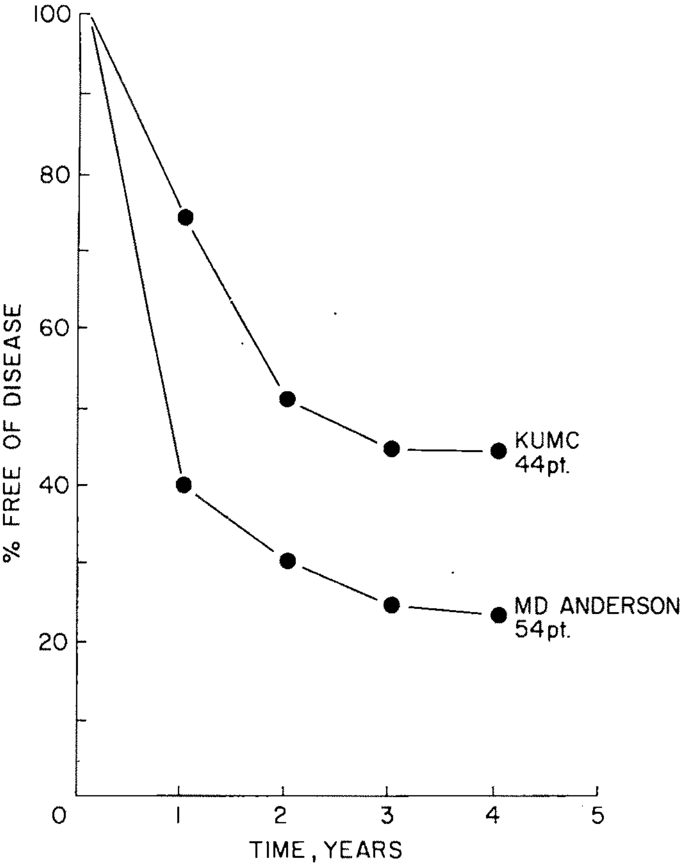

FIG. 3. Recurrence of melanoma in high-risk melanoma patients at KUMC versus control data from M.D. Anderson Hospital.

high-risk group (Fig. 2) appears to demonstrate increased survival over historic control levels.[10] This observation is substantiated further by an apparent decrease in recurrence rate compared to data reported by Gutterman et al.[5] (Fig. 3).

Preliminary results of the current study designed to evaluate the relative efficacy of V-II plus exchange versus LTF are shown in Table 3. Three patients have had complete disappearance of tumor in the LTF group but none of the V-II group have responded. All three LTF responses occurred in patients where autochthonous tumor was used for immunization. In the 6 nonresponders, autochthonous tumor was not available and allogeneic tumor was substituted. Every effort is now being made to obtain autochthonous tumor from patients randomized to the LTF group.

Immunologic Evaluation

Critical analysis of 32 consecutive patients with Stage III disease reveals that all 7 patients in this subgroup exhibiting response to immunotherapy were DNCB positive, and also had a positive response to at least one recall antigen prior to the onset of therapy. In those patients demonstrating unrelenting progression, only 5 of 25 were DNCB positive. However, only 4 of these 25 were negative to all recall antigens. Therefore, DNCB appears to be a better predictive test of response than recall antigens. All 44 Stage II patients had a positive DHR to DNCB.

Total lymphocyte counts, TDL and BDL data are presented in Table 4. It is apparent that patients with Stage III disease have a striking reduction of TLC, TDL, and BDL. Stage II patients also have decreased counts, but to a lesser degree than in Stage III.

Lymphocytes from 67 patients were tested for MIF activity (Table 5) in an attempt to correlate MIF activity with clinical course. Patients sequentially tested were scored as favorable if there was objective tumor regression or stabilization of disease for 6 months in Stage III disease or no recurrence in 1 year in Stage II disease. Progression of disease in shorter periods of time were scored as unfavorable. These data suggest that a sustained positive reaction or conversion of negative to positive correlates with a favorable clinical course, whereas a continued negative reaction or conversion of positive to negative predicts an unfavorable course. Because these tests were performed with allogeneic antigen no inference as to melanoma specificity is possible.

Discussion

It appears that immunotherapy can beneficially affect the course of patients with malignant melanoma. Clear regression of measurable tumor was seen in 24% of patients studied. It is doubtful that this overall response rate can be explained by "spontaneous regression." Survival is a difficult parameter to evaluate. However, comparison with historic control data appears to indicate

TABLE 3. *Comparison of Stage II and Stage III Patients Randomized to Treatment with V-II Plus Exchange of WBC or LTF*

	Number	Response
V-II plus Exchange of WBC		
Stage III	9	0
Stage II	8	—
LTF		
Stage III	9	3
Stage II	2	—

TABLE 4. *Peripheral Lymphocyte Counts in Patients with Stage II and Stage III Disease. Results are Expressed as Cell Counts/mm^3 ± One Standard Deviation*

	Number	Total Lymphocyte Count	TDL	BDL
Control	10	2736 ± 951	1455 ± 505	1195 ± 431
Stage II	44	2091 ± 556	1090 ± 392	859 ± 242
Stage III	32	1592 ± 727	631 ± 524	667 ± 303

TABLE 5. *Correlation of Clinical Response to Migration Inhibition Factor Data (67 Patients Tested)*

	Not Retested	Retest Positive	Negative
Positive 45 Patients	23	16 (7/9)*	6 (1/5)
Negative 22 Patients	9	9 (7/2)	4 (1/3)

* Values in parentheses represent the number of patients with a favorable clinical course over the number of patients with unrelenting progression of disease.

evidence of favorable response in Stage II and Stage III patients. The Stage II series reported has several unfavorable characteristics. There is a strong male predominence. Almost one half of the series consists of torso primary lesions with positive regional nodes. All head and neck melanomas were from the scalp or neck while over half of the control series head and neck lesions were from the face. Bias, therefore, in this group appears directed against the treated group.

On the other hand, the risk of treatment if present at all must be subtle. No untoward reactions to the therapy were noted, unlike BCG injection where serious reactions and even fatalities have been reported.[19]

It is discouraging that most of the Stage III patients ultimately developed progressive disease, and were put on chemotherapy protocols. The 42% of the 34 patients studied for survival alive at 2 years are of considerable interest. If there is any measureable survival at 5 years the interpretation of these data would be considerably strengthened. In many respects these results closely parallel those previously reported by Morton et al. despite the fact that they employ an apparently different concept of immune stimulation.[11] However, the possibility that the results obtained in this report were due to nonspecific stimulation rather than specific active or adoptive effects cannot be completely excluded. At this time there is no test system that will measure host antitumor activity specifically in the presence of nonspecific protein and HLA antigen effects that are probably evoked by allogeneic tumor vaccine preparations. The MIF data which demonstrated that most patients have activity initially and others can be converted by combined active and adoptive manipulation is of interest, but does not prove anti-melanoma specificity. Currently we are attempting to employ sequential skin testing as described by Burdick et al.,[1] lymphocyte blastogenesis as suggested by Vetto, et al.,[21] and MIF, using autochthonous antigen preparations to avoid the pitfalls of the allogeneic human system.

These data also support Morton's view that immune deficiency is a function of tumor burden. All of our Stage II patients were positive when tested for DHR to DNCB, compared to a 39% positive response rate in Stage III patients. Also, there is a clear decline of TLC, TDL, and BDL as the disease progresses. Conversely, response to immunotherapy appears related to a positive reaction to DNCB and increased levels of TLC[15] and, therefore, low tumor burden.

The results with LTF appear most interesting. As we have reported previously, the LTF patients had a higher response rate than the V-II plus exchange group.[8] In addition, all of the responses occurred where autochthonous tumor was used to cross-immunize the LTF donor partner. Also, the LTF patients had a higher conversion rate measured by MIF and conversion of recall antigen DHR than V-II plus exchange patients.[8] These results imply individual tumor specificity as has been suggested recently in colon tumors by Elias and Elias.[4] This critical point should be clarified as quickly as possible.

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DISCUSSION

DR. WARREN H. COLE (Asheville, North Carolina): I think their work is really very exciting, and I've been following it ever since they started it several years ago. Some of their important figures got a little bit lost in the numerous figures that Dr. Humphrey gave you. Therefore I would like to call your attention to page 13 in the program, where they say their one-year survival following immunotherapy is 100% versus 58% expected, and their two-year survival is 85% versus 44% expected. To me this is very remarkable, and indicates that immunotherapy has great possibilities.

In attempts to conceive of mechanisms to improve on the immunologic response, I have found it stimulating to speculate on the causes of the regression in spontaneous regression; and here I have been studying the 176 cases which Dr. Everson and I reported on several years ago. After studying these cases, I became convinced that the major cause was a stimulation, primarily accidental, of the immune reaction, which is only one of the many ways to obtain improved immunologic response.

Part of the work carried out by Dr. Humphrey and Dr. Jewell has been a stimulation of the immune system, but this is probably better illustrated by administration of BCG, which they have used, but I think Dr. Morton has probably used that much more extensively than anybody else.

There are several other known methods of stimulating a patient's immune response, and that's what gives me optimism, thinking we do have a few other ways of stimulating our immunologic response. I believe these various possibilities should be explored. These include other bacterial products, irradiated tumor cells, the enzyme neuraminidase, and a few others.

It's now obvious that one method of immunologic trial is effective in one patient and not in another. We are finding that out almost every day. Before we find a really effective mechanism, it appears that we might be justified in trying one method after another in a patient, until we find one which is reasonably effective. And this regimen would stimulate the procedure of trying numerous antibiotics to destroy an infection.

Anyway, its's very obvious to me that the immunologic treatment of cancer is now possible, and has great promise. So I would agree with that statement that Dr. Humphrey made just before he closed.

Obviously, we can't supplant the old reliables of surgery, radiation, and chemotherapy, but I believe we are about reaching the point where these can be supplemented by immunotherapy.

Now, the point of my remarks leads to an important question, which I would like to put to Dr. Humphrey and Dr. Jewell: Do they think that the immunologic treatment would be more effective in Stage I disease, given just after definitive treatment, such as operative resection of a tumor, when the patient still has some protective immunologic reaction of his own? Well, I really think so, but I'd like to ask the experts about this question.

DR. WARD O. GRIFFEN, JR. (Lexington, Kentucky): In the manuscript Dr. Jewell and Dr. Humphrey indicated that Vaccine I had a dose of 0.2 gm/ml of tumor, whereas Vaccine II had 2 gm/ml. Is the difference in response between V-I and V-II simply a dose response?

Secondly, no mention was made about debulking. I guess this is a corollary to Dr. Cole's question. If you can remove a great deal of the tumor, can you improve the ability of the patient to bring his own immunologic capacity into play?

And thirdly, do you think you are now ready to have randomized trials of your own various techniques of immunologic therapy, rather than to rely on comparing your data to historical controls, which is always fraught with danger?

DR. JAMES C. DRYE (Louisville): I think immunotherapy is a field which should be pursued. We have tried chemicals, radiation, and surgery, and I think this avenue is well worth exploring. The results of chemotherapy and surgery have been only partially successful. This immunotherapy approach may improve our results.

I arise to present a case of mine treated by an immunology method except I used blood from a patient who had been treated 8 or 10 years before and had no evidence of recurrence. I would first like to give the past history of my patient.

This patient had acute rheumatic fever at the age of about 12. This was followed by St. Vitus dance, or chorea, and apparently some injury to the heart. However, he had at the time I first saw him no symptoms of heart disease. At the age of 15 he had a thyroidectomy, and from the history it seems that he was severely toxic. He made a good recovery from this and takes 4 gm of thyroid a day. He developed petit mal at the age of ten or 12. This has been controlled by Dilantin and phenobarbital.

Several years ago the patient was vacationing in Rome, and a pop bottle which was being carried by blew up and tore out his right eye, and this was enucleated.

He came to me in March, 1967. He had a melanoma on the medial surface of the tibia about six inches above the ankle. I removed this with an excision biopsy with about a 3 mm margin, and it came back as melanoma on fixed sections. The next morning I removed about a 6 cm diameter of skind down to the periosteum, and took the fascia of the underlying muscle, and did a skin graft. This was in March, 1967.

In August of '67 he returned to me complaining of being short of breath. He had a flat percussion note and I could hear no breath sounds. I stuck a needle in his chest and removed 1500 cc of fluid. I was required to reaspirate him every five or seven days and removed 1000 to 1500 cc of fluid each time.

I injected nitrogen mustard, not a cancericidal dose, because I had begun to believe that chemotherapy agents were practically useless; all they did was make a patient sick. But I hoped to obliterate the pleural space, so that he would not get this collection of fluid, and breathe better; but this didn't work either.

By then I has become quite fond of this patient, and I lay awake at night thinking; What can I do? There ought to be something.

Dr. Condict Moore, who is a member of this society, had a patient who was operated on for melanoma eight years before and apparently recovered. I transfused 250 ml of blood from this patient to my patient at the same time removing another 1500 cc of fluid from his chest. I repeated the transfusion a week later. This patient never again had any pleural fluid collection, and became completely asymptomatic.

In August of '68 he developed evidence of heart failure due to mitral stenosis from his rheumatic fever. Dr. Allan Lansing, of Louisville, operated on the man. There was no evidence of any pleural involvement, and nothing in the lungs. The x-rays at the time I first saw him were highly suggestive of a mass in his left upper lobe. Dr. Lansing could see or feel nothing, and the patient recovered from his heart operation.

I saw this patient ten days ago. He is alive, well, healthy and doing well. He has no symptoms.

Honestly and very humbly, I don't know whether I cured a diagnosis or cured the disease, and that it may recur. We all know that melanoma is extremely unpredictable. This man might have gotten along as well without any treatment. I really don't know.

DR. WILBUR C. SUMNER (Jacksonville, Florida): Since Dr. Humphrey has mentioned Sumner and Fouraker, I though I might give you the results of our paper that we reported several years ago.

Ruby was the first patient who made a spontaneous remission from melanoma. I have seen Ruby recently, and she is still going strong, although she has also had one baby since we reported her case, and she stayed away for five years, because she was afraid to come in.

Jack, who received Ruby's blood, did live for seven years, with complete remission from melanoma. He died of nephrosis, not from melanoma.

Jack showed a complete regression of melanoma after receiving Ruby's blood, from a histological standpoint.

DR. HIRAM C. POLK, JR. (Louisville): I apologize for rising before such an erudite group to make a fairly simple point. I would remind you that the rates of regression shown in this presentation by Dr. Humphrey and Dr. Jewell do not greatly exceed the spontaneous remission rate for melanoma, and that, perhaps taking disagreement with Dr. Humphrey's closing point, I think that groups of three, four, and seven are hardly sufficient to put to rest any doubt about the role of immunotherapy.

I personally believe this is promising work, and there is good data being collected, but I think it's extremely premature to couch those numbers with those kinds of interpretations.

DR. W. R. JEWELL (Closing discussion): I don't think that we're ready to deal with Stage I disease yet. I don't think that we have excluded the risk factors of immunotherapy enough to do that. But I would want to show just one brief set of slides, to show where Dr. Cole may be a little bit ahead of both Dr. Humphrey and me, and all the rest of us, for that matter. (Several slides were shown.)

The point of all this is that, as the disease progresses, the T cells seem to drop off, the B cells seem to drop off, and therefore the total lymphocytes drop off. We have shown this in a number of other test systems as well. So perhaps we should treat Stage I disease while immune competence is still present.

Dr. Griffen's questions about the type of vaccine, I think, are very relevant. That's why we went to Vaccine II, because we wanted to have a stronger antigenic preparation, if you will; and as he pointed out, there are 2 gm/ml in that, and 0.2 tumor gm/ml equivalents in the other. I don't known whether that's why we're seeing a little bit better response with it. We'd like to think so.

The debulking concept: If you will remember the slides, the difference between the UCLA data and our data in Stage III tumors may be due to the fact that Morton and his group routinely debulk patients with Stage III disease. We don't do that. We just treat them with immunotherapy.

As far as a randomized trial is concerned, I think it would be an ideal thing, and I wish we had nil controls. It's very difficult to get that started. Everybody thinks, "That's a silly thing to say", but it really isn't. It's a very hard thing. It's hard to sell to our patients; it's hard to sell to our referring doctors. And I'm afraid that if we did start a nil control group, it would be very difficult to arrange.

I'm hoping Morton will finish up his randomized study with BCG, versus nil controls. If benefit from immunotherapy is maintained, we can take his treatment arm, randomize it against our two treatment arms, and we won't have to have a nil control group. I hope that's what will happen.

Dr. Drye's case I thought was most interesting, and I think it's cases like that which really started us doing these kinds of clinical experiments.

Dr. Sumner, I enjoyed your remarks. I have read your work, and I think there again is another instance of why we're here tonight.

Dr. Polk, I think, as always, managed to throw a very sobering thought into something that looks very good. I would hasten to add that our point of view is not all that much different from his. We don't regard this as a final answer. I don't think immunotherapy is something that must be given to every patient that has melanoma, or it's malpractice not to. We don't feel that way at all. I think it is promising. I think it must be studied further. I think now we have to look for better ways of doing immunotherapy, get better laboratory tests, so that we can monitor our responses, and we're going off in that direction.

Dr. Sutherland's remarks on irradiated cells were important. I'll be very pleased to look at their results when they have them. I hope they come out to be the same as ours.

The Surgical Treatment of Carcinoma of the Colon and Rectum:

An Index of Quality Care and Sociologic and Geographic Distribution

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A comparative experience with 474 patients with primary carcinoma of the colon and rectum has been evaluated in several hospital settings, with particular respect to patient populations, geographic distribution, and surgical characteristics. The differences and similarities are interpreted with caution but may provide a format by which significant objective determinants become the basis for subsequent assessment of quality care in an illness which is prevalent and amenable to relatively standardized operative management. No difference in quality of medical care provided was detectable across the sociologic and geographic boundaries studied. Notable increases in extent of neoplasm and severity of co-existent illness in the urban, "indigent" population adversely influenced both short and long-term mortality rates.

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ALTHOUGH MEDICAL FASHIONABILITY poses a host of challenging and changing problems, certain old problems and older diseases continue to vex the surgeon. Among these is carcinoma of the colon and rectum, which remains a major source of morbidity and mortality in Western society. Indeed, for 1975 an estimated 99,000 Americans will have acquired the illness and some 49,000 will die from it.[1] Contrary to common belief, there has been relatively limited progress in the control of this prevalent disease. Partially responsible for this misconception may be the fact that rehabilitation of the patient treated for carcinoma of the colon, even if treated unsuccessfully, is often highly effective.[6]

As a result of separate studies,[3,7] it was concluded some time ago that the increased survival rate among patients with carcinoma of the colon and rectum could be attributed entirely to two fairly simple improvements. First, the increase in operability and resectability reflects increasing sophistication of surgical practice related to advances in anesthesiology and supportive care as well as improved technical skill and enhanced awareness of certain biologic characteristics of large bowel cancer on the part of the surgeon. Second, good indirect evidence exists that patients generally come to treatment earlier in the course of their illnesses than was true four decades ago.

An equally impressive determinant of improved survival has been a decreased hospital treatment mortality. In other words, more patients are coming to operation for their colon cancer, more patients are undergoing resection, and fewer patients are dying from the effects of the attempted operative treatment, thereby yielding a significantly increased number of patients who have had successful primary treatment and who are eligible to benefit from control of the disease process. However, the more extensive excision including lymph nodes and adjacent organs has not yet been reflected in increased over-all survival rate, although no doubt in isolated cases these represent an enormously effective way of dealing with certain problems.

Clinical Experience

Specific studies of factors which are real and apparent determinants of increased mortality risks after operations

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TABLE 1. *Some Factors Influencing Operative Mortality for Colorectal Carcinoma*

Positively Correlated*	Not Correlated†
Age > 69 years	Max tumor dimension > 7 cm
Heart disease requiring digitalis	Length of resected bowel
Resection in presence of an inflammatory mass	Multiple organ resections
Resection for palliation	Antimicrobial bowel prep
Fewer than 10 regional nodes resected	Lymph node metastases

* $P \leq 0.03$.
† $P > 0.32$.

in 474 patients with colorectal cancer were carried out to analyze survival rates. Table 1 restates those factors which were and were not associated with significant changes in the risk of operation for carcinoma of the colon in one institution over the period 1940–1951. The purpose of this presentation is not simply to restate the principles and problems involved in the management of large bowel cancer but to examine these facts in light of current social, economic and political considerations related to the quality of medical care and its distribution across both geographic and sociologic boundaries.

To accomplish this, we studied in detail 474 patients from 5 identifiable social and medical situations. The first is a city-county hospital (Hospital A), in which virtually all patients are considered medically indigent and which represents the primary educational facility for our school of medicine. The second institution is a representative Dean's Committee Veterans Administration facility (Hospital B), which has been closely affiliated with the same medical school throughout the period under study. The staff are full-time members of the university department of surgery, with a resident staff identical to that functioning in Hospital A. Hospital C is a large community hospital which had been operated as a charitable institution with an approved residency program unaffiliated with the university. *Subsequent* to the completion of the period of study, this institution has undergone several changes, including disbanding of its residency program in favor of full affiliation with the university and transferring its operational status from a charitable institution to an investor-owned one. The surgical staff involved in the institution is largely Board certified, frequently but not always having trained in the region. The majority of those individuals who are not Board-certified surgeons are fellows of the American College of Surgeons. Hospital D has been a major community hospital throughout its history with an independent, limited residency program allowing 2 years of accredited training toward Board certification in surgery. The staff involved in the period under study were uniformly certified by the American Board of Surgery and were Fellows of the American College of Surgeons. Just before the period studied, Hospital D developed a close, significant affiliation with the department of surgery of the university, which encouraged increased participation by the full-time medical school faculty in practice within the institution. The resident staff became homogeneous with the other three institutions mentioned (A,B,C). The data from Hospital E reflect a 30-year personal experience of a Board-certified surgeon in a nearby city with a smaller population. House officers have not participated in the care of these patients; other staff members of the institution have been variable in terms of certification and fellowships.

The following parameters were compared within these hospital settings: 1) frequency and severity of significant co-existing disease; 2) extent of the primary tumor itself; 3) rates of operability and resectability; 4) frequency of hospital deaths after operative treatment of colorectal cancer; and 5) long-term survival. The comparisons also consider that patients cared for within the larger city (Hospitals A through D) include a clearly indigent group of patients at the city-county hospital, an intermediate group of patients at the Veterans Administration facility and a third and substantially different socioeconomic group in Hospitals C and D. The comparison in Hospital E includes a patient population similar to those in Hospitals C and D but cared for in a substantially smaller community with less complete supportive services available.

The results of our study with respect to the frequency of co-existing diseases (Table 2) is perhaps more accurately expressed by a frequency distribution for number and severity of those diseases in Table 3. A clear preponderance of patients with multiple associated, severe diseases was among those seen in the city-county hospital setting. This no doubt influenced operability, resectability and hospital mortality adversely. Intermediate distribution of such patients occurred at the Veterans Administration Hospital. All of the private hospitals had about the same proportion of patients with significant co-existing diseases.

Table 4 reflects an assessment of extent of neoplasm

TABLE 2. *Frequency of Co-existent Significant Illness*

	Patients	
Hospital	Total	With Disease
A	98	54 (55%)
B	106	54 (51%)
C	108	50 (46%)
D	101	46 (46%)
E	61	25 (41%)
	474	229 (48 ± 2%)*

* Estimated probability ± 1 S.E.

TABLE 3. *Frequency Distribution of Serious Associated Diseases*

Hospital	Total Patients	Patients With a Given Number of Associated Diseases 0	1–2	3–4	5–6	7–8	9–10
A	98	21	32	24	12	5	4
B	106	44	33	22	6	1	0
C	108	58	27	14	5	3	1
E	61	35	18	6	2	0	0

at the time of diagnosis and treatment of the primary illness. For simplicity, a weighting scale was adopted in which Dukes' A tumors are classified as 1, Dukes' B as 2, Dukes' C_1 as 3, and Dukes' C_2 as 4. A measurable number of patients at the city-county hospital could not be classified because of judged inoperability; these patients were arbitrarily assigned to the Dukes' C_2 classification. Table 4 shows the substantial differences across the patient populations with respect to stage of disease at the time definitive medical care was first achieved. The patient population at the city-county hospital is significantly more ill from their cancer than are those in the Veterans Administration Hospital and Hospital C. Somewhat more favorable outlooks for patients with malignant neoplasms existed in Hospitals D and E.

Our survey dealt with the *initial* diagnosis of carcinoma of the large intestine; therefore, operability can be determined as the proportion of patients diagnosed who underwent operation of some sort. Operability rates were dramatically lower, as indicated in Table 5, for patients cared for in the city-county hospital setting and distinctly different from those seen in the other hospitals.

We did not attempt the often specious distinction between resection for cure and resection for palliation. The rate of resectability varied significantly, with the lowest resectability rate in the city-county hospital population, and next lowest among patients operated upon at the Veterans Administration Hospital. However, resection was possible substantially more often in Hospitals C and E and of intermediate accomplishment in Hospital D. Statistically, the 5 institutions show significant lack of homogeneity with respect to frequency of resection, although the bimodal distribution (Hospitals A and B low, D intermediate, and C and E very high) defies designation as to which of the hospitals is largely responsible. Table 6 compares hospital mortality with respect to operability and resectability. Despite the many variables between and among the institutions studied, there is remarkable uniformity of hospital mortality rates among those qualifying for operation and then, subsequently, resection.

A major determinant of over-all outcome, operative mortality did not differ significantly among the institutions studied, although the rate is measurably higher than described in prior reports from other institutions. By contrast, the current prospective study of preoperative irradiation for rectal cancer in Veterans Administration Hospitals indicates a similar mortality for the patient population.

More limited studies of long-term survival, with respect to the so-called 5-year "cure," were undertaken in each institution; these data are shown in Table 7. The startlingly low crude 5-year survival in the city-county hospital is more nearly comparable when expressed as survival among those undergoing resection, suggesting again that the poor results in that hospital are more nearly related to the severity of both co-existent illness and the primary neoplasm than to other factors.

Discussion

The data presented in this review show a striking similarity of co-existing diseases, extent of carcinoma, operability, resectability, and mortality after treatment for all of the patients classified as private without respect to geographic location. The two communities included in this study were disparate with respect to number of inhabitants but geographically proximate. No geographic difference in quality of care available to individual patients with colorectal cancer could be assigned. We realize that the selection of an experienced and certified surgeon in the smaller town prejudices the conclusion to some degree. However, the surgeons working within Hospitals C and D were similarly selected. These kinds of data, when expanded and carried to other logical conclusions, must speak to the availability of quality care on a geographic basis and, by inference, to the allegations of maldistribution of surgical skills.

Although we did not identify geographic differences, there are striking, persistent and impressive differences among those patients cared for in the city-county hospital and who were predominantly from a different socioeconomic order than those cared for in Hospitals C, D, and E. Interestingly, in many respects the Veterans

TABLE 4. *Extent of Primary Neoplasm*

Hospital	Dukes' A	B	C_1	C_2	Unclassified	Weighted* Estimate
A	3	26	19	33†	17†	3.2
B	2	28	32	37	7	3.1
C	6	40	18	40	4	3.0
D	4	38	29	27	3	2.8
E	4	27	13	17	0	2.5
Total	19	159	111	154	31	

* Dukes' A = 1; B = 2; C_1 = 3; C_2 = 4; Unclassified = 4.

† Advanced disease more prevalent at Hospital A, $P < 0.05$.

TABLE 5. *Operability and Resectability*

Hospital	Diagnosed	Operated	% Diag.	Resected	% Diag.†	% Operated†
A	98	78	80*	65	66	83
B	106	100	94	80	75	80
C	108	99	92	96	89	97
D	101	93	92	81	80	87
E	61	60	98	58	95	97

* Significantly different from other hospitals, $P < 0.01$.

† There is significant lack of homogeneity between hospitals, $P < 0.01$.

Administration population falls in between these extremes. The experiences are indeed most difficult to compare. However, when considering only those patients who are in adequate general physical good health and whose carcinoma is sufficiently limited to warrant resection for cure, the quality of care offered in the city-county hospital is identical to that offered in the private hospital settings (Tables 5 and 6). In other words, those determinants of early and late outcome (i.e., hospital mortality and 5-year survival rates) are so similar as to be relatively reassuring about the absence of differences in quality of care provided for the disparate patient groups.

The interpretation of relative deficiencies of certain aspects of health care to underprivileged populations is difficult. The city-county hospital studied here has pursued an open-door policy with no attempt whatsoever to screen patients according to their ability to pay. The only requirement for care is to present oneself to the door of the hospital. That hospital has, however, been operated with many of the adverse esthetic effects of such an institution—a relatively meager physical facility is appropriately staffed but lacks the amenities of hotel care. Furthermore, the out-patient clinics do not operate with an appointment system, nor can a patient count on seeing the same doctor consistently, although this is feasible for at least a relatively short period.

Although the over-all quality of the environment and the endeavor can be enhanced, a major apparent divergence of results between patients cared for in indigent and in private situations may be encountered. An inevitably much-overlooked component of health care is the patient's responsibility for himself; restated, that means the accountability the patient must assume to seek medical care given reasonable signs of significant illness. Much thought has been addressed to this point. A variety of factors influence the frequency and promptness with which patients with given signs and symptoms seek medical care. But virtually none of these may be attributed to the absence of available care or to differences in the quality of medical assistance provided. Stated concisely, many differences exist in the educational, attitudinal and general responsiveness of patients seeking care in these differing institutions.

Although the patient surely must accept a part of the responsibility for some of the differences outlined above, many of the determinants of operative mortality are physician related. A retrospective study does not allow the proper assessment of the many parameters involved in survival or nonsurvival during hospitalization. There was remarkable homogeneity in the patient population studied, given similar stages of tumor and with some adjustment for frequency and severity of co-existing disease. The disturbing observation is that hospital mortality was consistently higher than that described from institutions in which larger numbers of operations for cancer of the large bowel were done on a regular basis.[7,9,11,12] Although we have no data to support the point, further refinement of mortality may be a function of volume. More importantly, one must begin to assess the operative management of colonic cancer in an objective fashion, so that we can be as certain as possible that extraneous or preventable factors are minimized. Although emotionally unattractive to some surgeons, the program described by Knutson and Watson[5] regarding a simple, logic (judgment) tree for the intraoperative management of cancer of the colon has much to recommend it as a framework within which to evaluate the consistency and excellence of operative care in a given institution—in addition to being used as a prospective advisor and consultant by the surgeon in the judgmental phase of a given operation. As indicated previously, the data reviewed herein do not allow definition of these differences. Suffice it to say that the mortality rates reported are almost identical with those coming from the combined study by the Veterans Administration[4]

TABLE 6. *Comparative Hospital Mortality Rates*

Hospital	Among Patients		
	Diagnosed	Operated Upon*	Rejected†
A	32/98 (33%)	17/78 (22%)	8/65 (12%)
B	22/106 (21%)	19/100 (19%)	11/80 (14%)
C	12/108 (11%)	11/99 (11%)	10/96 (10%)
D	14/101 (14%)	12/93 (13%)	8/81 (10%)
E	11/61 (18%)	10/60 (17%)	8/58 (14%)

* Comparison using weighted differences shows the hospitals to be homogeneous with respect to hospital mortality among patients operated upon. For all hospitals, there is a significant difference in hospital mortality between patients operated and not operated upon ($P < 0.01$).

† Comparison using weighted differences shows the hospitals to be homogeneous with respect to hospital mortality among those patients whose tumors were resected. For all hospitals, there is a significant difference in hospital mortality between those patients resected and those not resected ($P < 0.01$).

TABLE 7. *Five-year Survival Data*

Hospital	Eligible	Alive & Well	% Eligible	% Resected
A	49	9	18	30
B	52	14	27	34
C	54	18	33	37
E	61	23	38	40

but still significantly greater than have been reported by one of us for extended, multi-organ resections in selected patients.[8]

In similar settings, it is entirely possible that someone with a special interest in colorectal cancer can achieve operative mortality rates that are quite low while dealing with significantly challenging cases. Surely, for the periods and places studied no one person evolved a special interest in and/or referral base for patients requiring operative management of carcinoma of the colon and rectum. On the other hand, one of the authors has recently tabulated his experience of 142 consecutive personal patients treated for carcinoma of the colon and rectum, among whom there was one hospital death. Generally, these patients manifested relatively extensive carcinoma (3.2, Table 4) but a relative absence of coexisting diseases (Table 3). Just as was apparent from the study undertaken to define the frequency of halothane-associated hepatitis,[10] the present study indicates that there are real and probably significant differences between surgeons and between institutions with respect to the frequency of death after operation for a given procedure in a patient with a given degree of primary and associated illnesses. Just as the halothane study was unable to define reasons for the differences within institutions and differences among operations within a given institution, neither can we specify causes. The authors' strong opinion is that, if errors can indeed be identified, they are more often judgmental than technical and that improvements might appropriately be directed to both input and outcome of the process.

The foregoing notwithstanding, objective criteria, such as those used in this study with particular emphasis upon adjustment for the frequency of associated diseases and the extent of the primary disease process, will allow the most meaningful evaluation of quality of patient care. If we are to justify our accountability, evaluation must not be based on subjective assessments by one's colleagues, friends and peers. Objective criteria must be used in every instance, and standards of assessment must reflect as accurately as possible the patient situation without the benefit of 20/20 hindsight. Indeed, studies such as these and the development of *objective* assessment systems will do much to protect our patients and the profession from inappropriate and ill-advised analyses by individuals with limited or no medical background. However, the inherent limitations of measurement in a situation where no two aspects of a single illness are identical is sufficient caution. Devitt has outlined particularly clearly the special problems of the ultimate application of this concept in the surgical setting.[2] We must undertake these analyses, but with care to look beyond first order conclusions, to existing biases as well as possible professional and public misinterpretation.

Nevertheless, the data examined and reviewed in this report are strongly indicative that the sharply different indices of care are primarily a function of the population served, with its specific social and health related characteristics. The definable medical parameters influencing the outcomes assessed appear to be of second order importance, although very likely capable of improvement.

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DISCUSSION

Note: Some of the discussants' remarks refer to both this paper and to the one following by Dr. Stephen M. Wilson.

DR. GEORGE A. HIGGINS, JR. (Washington, D.C.): I should like to congratulate Drs. Baughman and Polk and their group for combining results in a major surgical disease with the matter of quality care assessment. Whether we like it or not, we are all going to be faced increasingly with the matter of comparing our results within our individual hospitals and also comparison of results between all hospitals even though they may draw vastly different groups of patients and be located in different geographic areas. It is very important to realize that there is a vast difference in patient groups, even in the same geographic area, as so well shown by Dr. Baughman; but also as one listens to these two excellent presentations, it is obvious that the patients presented are quite dissimilar.

Even so, if we are going to compare our results, it is most important that we develop standard criteria and parameters. For example, what are surgical mortality rates? Dr. Baughman spoke of hospital mortality, while Dr. Beahrs spoke of operative mortality, not stating what he meant by this as regards time. Our group along with most of the large cooperative groups have adopted an arbitrary 30-day operative mortality figure so that at least we are all using the same yardstick. So here we have three different definitions of what should be a relatively simple and uniform unit of measurement.

The Veterans Administration Surgical Adjuvant Group has examined a series of 1064 patients having colon resection. You might note that this is a slightly larger number than presented by Dr. Beahrs, although it took the combined data from a large number of hospitals to do this. In this analysis, we examined 71 criteria and characteristics which might be expected to influence survival, both the 30-day survival and the long term survival. For the 30-day mortality, we found seven factors out of the 71 which influenced survival significantly, and six of these had to do with postoperative complications. The only one that was not a postoperative complication in our group was age of the patient at the time of operation.

(Slide) This depicts the 30-day mortality based on age by decades and as one can see above the age of 70, the 30-day mortality increases greatly. You will also note that our overall 30-day mortality was between that reported by Dr. Baughman and the series from the Mayo Clinic. In this study, only those patients having a so-called "curative" resection, in which no obvious residual was left behind, are included.

(Slide) This shows 30-day mortality based on a number of factors which one might expect to influence this adversely but as can be seen, the only one that had a significant influence was that patients having abdominal perineal resection had a slightly higher mortality than those having other types of resection.

(Slide) This slide shows the factors which influence long term survival. As can be seen most of these are concerned with the extent of disease, that is involvement of adjacent lymph nodes, serosal involvement, blood vessel invasion, lymphatic invasion, or involvement of other resected organs. This of course is essentially the Duke's C group although blood vessel and lymphatic invasion are not included in the Duke's classification. The only other factor which influenced long term survival in those patients was somewhat less than in patients having lesions in the remainder of the colon.

Again I would emphasize the great hazard in comparing one hospital with another because of the vastly different patient groups. We have found in our cooperative group that even historical controls in a study group that has had continuous experience over the past 18 years are unreliable. As an example of this (slide) we have survival for patients having resection for lung cancer. The heavier line is our current study showing a significantly better survival than the lighter line showing survival from previous protocols. This certainly does not mean that our surgical care is better but rather that more of these patients are being operated at an earlier stage of disease, when the lesion is localized to the lung. Also, with more extensive screening of patients preoperatively, fewer patients who already have occult metastases are being operated upon.

Lastly, I would like to emphasize one statement in the manuscript which Dr. Polk so kindly sent to me, and I quote: "An inevitably much overlooked component of health care is the patient's responsibility for himself." Much too often patients have delayed inordinately long in seeking medical care or coming to the hospital and the cancer has spread beyond surgical retrieval. In addition, I think there is general agreement that lung cancer is largely a self-inflicted disease and this is very likely true for cancer in a number of other locations. Better public education and better acceptance of what we know about cancer prevention can be a potent factor in reducing the over-all death rate from cancer.

DR. HIRAM C. POLK, JR.: (Closing discussion) I think, to clear up any confusion, we'll have to define the groups we're talking about tonight. We're simply discussing, in our experience, all patients who were diagnosed to have cancer during this period of time. You know how one can make one's numbers look better by going from all diagnoses to all patients operated on, to all patients resected, to all patients resected for cure; the numbers get better and better.

I would differ with Dr. Letton. The outcome for unselected patient populations who come into almost any hospital in America with cancer of the colon or rectum has never achieved a 50/50 survival. It is significantly lower, and has consistently been reported as such, as long as you take all comers.

Dr. Higgins was very kind to restate our thesis, and I think he's exactly accurate. If peer review is going to be with us, it's very important that that peer review be assessed in an objective way, on data that are expressed in some reasonable outcome; i.e., hospital mortality rate. It is, therefore, all the more important to be certain that the patient groups that you compare are equal with respect to co-existing disease and equal with respect to extent of their cancer.

As far as we can tell in these rather disparate groups, only the urban indigent population is significantly different from the others, and that, indeed, as a whole, almost totally accounts for all of the differences defined among these groups.

Let us hope, if we must face this, we use these kinds of objective measurements of our own work as a way to begin what is surely going to be a major task, and one by which our responsibility will be largely judged.

The Curative Treatment of Carcinoma of the Sigmoid, Rectosigmoid, and Rectum

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This retrospective series comprises 902 patients who underwent curative resection of the sigmoid colon, rectosigmoid, and upper rectum at the Mayo Clinic during the years 1959 to 1969. Lesions were divided according to the location from the dentate line, with 346 patients having had a lesion located more than 20 cm from the dentate line; in the remaining 556 patients, the lesion was between 6 and 20 cm distant. A thorough analysis was undertaken comparing these two groups of patients on the basis of operative mortality and morbidity, including anastomotic complications, 5- and 10-year survival, and incidence of local recurrence. Overall operative mortality was 1.9%, with an 8.1% incidence of anastomotic complications. The overall 5-year survival rate was 72% and the 10-year survival rate was 55%. The incidence of anastomotic recurrence for anastomosis performed with the use of extraperitoneal rectum was 5.8%; recurrence at the suture line developed in 2.9% of patients who underwent anastomosis to serosa-covered bowel.

In addition to the above data, information will be presented which demonstrates the effect of the patient's height and weight on the surgeon's ability to perform a low-anterior anastomosis. Finally, the incidence of anastomotic complications and of local recurrence were analyzed according to the intestinal preparation employed, the use of parenteral antibiotics, and the method of drainage used near the anastomosis.

THE CHOICE of treatment of carcinoma of the upper rectum and rectosigmoid remains a controversial subject. Because the incidence of carcinoma of the colon is constantly changing,[14] it becomes increasingly important for the surgeon to be aware of the results of each therapeutic endeavor he undertakes. Naturally, the major objective of any cancer procedure is to provide the greatest opportunity for survival with minimal morbidity and long-term inconvenience.

The major controversy in the treatment of carcinoma of the rectosigmoid colon and upper rectum involves the indications for the low anterior resection, transsacral resection, abdominal endorectal resection and the combined abdominoperineal resection. The expected results from these procedures are well known.[7] It has previously been demonstrated that tumors located in the mid and lower parts of the rectum are best treated by the combined abdominoperineal resection. When the tumor is amenable to resection transabdominally, the result is an essentially normal bowel function. However, it is necessary to know whether the patient is liable to an increased risk of anastomotic and pelvic recurrence. In addition to survival rates, postoperative morbidity and mortality should be comparable to those following the combined abdominoperineal resection.

The object of this retrospective review is to provide data on the end results of low anterior resection. This operation will not be compared with the Miles procedure as is usually done[18]; instead, it will be compared with the standard anterior resection used for the removal of carcinoma of the sigmoid colon, to determine whether the end results of operations for removal of carcinoma in the rectosigmoid colon and upper rectum are similar to the end results of operations for the removal of cancer in the sigmoid colon. For such an evaluation, these operations should be comparable not only in operative mortality, morbidity, survival and recurrence rate, but they should also have been undertaken for tumors of similar cell type, grade and stage and relatively similar on the basis of clinical presentation.

In the performance of low anterior resection, it has long been thought that because of the anatomic configuration of the true pelvis, the close adherence of the sacrum posteriorly and the prostate or vagina anteriorly pre-

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TABLE 1. *Series Composite*

Operation	No. of patients	Males	Fe-males	Age (avg, yr.)	Height (avg, in.)	Weight (avg, lb.)
Anterior resection	346	180	166	62.88	64.2	153.68
Low anterior resection	556	295	261	62.81	62.8	151.02
Total	902	475	427	62.84	63.2	152.04

Differences between these categories are not statistically significant for the two operative groups.

TABLE 2. *Preoperative Symptoms*

Symptom	Low anterior resection (556)	Anterior resection (346)	Significance of difference
Bleeding	380 (68.3%)	203 (58.7%)	$P < .005$
Obstruction	14 (2.5%)	9 (2.6%)	NS
Pain	73 (13.1%)	86 (24.9%)	$P < .001$
Change in bowel habit	165 (29.7%)	82 (23.7%)	NS
Anemia	35 (6.3%)	40 (11.6%)	$P < .006$
Weight loss (>5 lb)	137 (24.6%)	79 (22.8%)	NS

vents a radical resection of tumors in this area.[13] In addition, because of the lack of peritoneum covering the rectum and the technical difficulties imposed by the narrow pelvis, anastomoses in this area are less secure. These same problems do not exist when resection of the sigmoid colon is undertaken for carcinoma. The sigmoid is located on a long mesenteric pedicle, and therefore lends itself to radical resection, and anastomoses in this area are also less difficult to accomplish.

The sigmoid, rectosigmoid and upper rectum share a similar vascular and lymphatic supply. Therefore, end results of resections of these areas might be the same. Because the sigmoid, rectosigmoid and upper rectum share the same stool consistency and bacteriologic flora, anastomotic problems might also be similar on these bases.

Comparison of low anterior resection and anterior resection in terms of survival, local recurrence and anastomotic problems provides data to support the use of low anterior resection in the treatment of carcinoma of the rectosigmoid and upper rectum. Unless low anterior resection is inherently a poor cancer operation, the similarity of these results would suggest that the only essential differences between anterior resection and low anterior resection are technical difficulties; and it would add further justification to the use of the low anterior resection in preservation of normal anal function.

Methods and Materials

A total of 1,193 case histories of patients subjected to anterior resection for carcinoma of the sigmoid colon and low anterior resection for carcinoma of the rectosigmoid and upper rectum from 1959 to 1969 were reviewed. Anterior resection was used for all lesions of the sigmoid colon located farther than 20 cm from the dentate line as measured with the proctoscope and in which peritoneum was present both proximally and distally at the anastomosis. Low anterior resection was used for all lesions less than 20 cm from the dentate line in which the anastomosis to the extraperitoneal rectum was performed transabdominally. Excluded were all patients who underwent these operations for lesions other than colonic carcinoma (29 cases), for recurrent colonic carcinoma (11 cases), or as palliative resection for colon cancer that was metastatic at the time of the original procedure (which included 109 cases of sigmoid carcinoma and 142 cases of carcinoma of the rectosigmoid and rectum). Therefore, the definitive series included only those patients who had undergone a curative resection for colonic carcinoma of the sigmoid, rectosigmoid, and upper rectum.

Vital Statistics. The definitive series thus comprised 902 patients, including 346 with carcinoma of the sigmoid colon and 556 patients with carcinoma of the rectosigmoid and rectum. The ages varied from 15 years to 92 years with an average age of 62.8 years. Table 1 demonstrates the range of patients' ages for the major groups of anterior and low anterior resection. There were 475 men in this series and 427 women.

Symptoms: Type and Duration. The most common complaints of patients with colonic carcinoma are rectal bleeding, pain in the abdomen or anus, change in bowel habits (either diarrhea or constipation), change in stool caliber and bowel obstruction (Table 2). In 10 to 11% of these patients there were no symptoms preoperatively and the diagnosis was made during a routine performance of either colonic roentgenography or proctoscopy (Table 3).

Patients with colonic carcinoma complain of symptoms referrable to the colon for variable periods of time, from weeks to years. Because of the difficulty in pinpointing the initiation of symptoms in most patients, they were categorized broadly as shown in Table 3.

Associated illnesses, the most frequent of which were diabetes mellitus, heart disease and chronic obstruc-

TABLE 3. *Duration of Preoperative Symptoms*

Duration	Low anterior resection (556)	Anterior resection (346)
Asymptomatic	58 (10.4%)	40 (11.6%)
<3 mo	173 (31.1%)	108 (31.2%)
≥3 mo	325 (58.5%)	198 (57.2%)

Differences between operative groups are not significant.

TABLE 4. *Broders' Classification*

Grade of lesion	Low anterior resection (556)	Anterior resection (346)
1	86 (15.5%)	71 (20.5%)
2	421 (75.7%)	254 (73.4%)
3	45 (8.1%)	19 (5.5%)
4	4 (0.7%)	2 (0.6%)

P for differences between operative groups <.023.

tive pulmonary disease, occurred in approximately 5% of the patients and were evenly distributed between the groups of patients undergoing anterior resection and low anterior resection.

Diagnosis. All of the tumors were diagnosed by barium contrast roentgenography or proctosigmoidoscopy. Most lesions that were 8 cm or less from the dentate line were palpated by digital examination of the rectum. Anemia (hemoglobin concentration of less than 11 g/dl) was diagnosed in 8.3% of the entire group. Because of the extreme rarity of a positive finding from liver enzyme determinations or scintillation liver scanning, these diagnostic procedures were not evaluated in this series.

Pathologic Data. The cell type for all of these lesions was adenocarcinoma. For both operative groups the lesions were classified according to the methods of both Broders and Dukes (Tables 4 and 5). Seventy-three patients had tumors that had invaded the adjacent organs but were still resectable. This included 15 patients with involvement of the small intestine, 23 patients in whom the bladder was affected, and 35 who had involvement of the left lateral peritoneal wall or in whom local perforation occurred with formation of an abscess cavity (Table 6).

Results

The data obtained from this study were analyzed in several ways. Among the most important results are those concerning the operative morbidity and mortality, the long-term survival and the cause of treatment failures, especially those due to local and pelvic recurrence.

Operative Mortality. In this group of patients undergoing resection of the colon and rectum for cure, 17 (1.9%) died after the operation (Table 7). This included 6 of 346 (1.7%) patients who died after anterior resection and 11 of 556 (2.0%) who died after low anterior resection. The operative mortality for patients who were more than 70 years old was 3.1%. The causes of death are detailed in Table 8. There was no significant difference between the groups in this respect.

The most serious complication after bowel anastomosis is a breakdown in the suture line. Actual disruption of the anastomosis occurred in 12 patients undergoing low anterior resection and 8 with anterior resection. However, in patients treated by low anterior resection, fecal fistula developed in 37 (6.7%) of the cases and anterior resection was followed by fecal fistula in 15 (4.3%). The total number of anastomotic problems, then, was 9.0% of the low anterior resection group and 6.6% after resection of the sigmoid colon.

Because various surgeons using different approaches were involved in this study, the use of antibiotics parenterally or in conjunction with mechanical preparation of the bowel varied considerably throughout the series. The bowel preparation was otherwise standardized and consisted of laxatives, enemas and a low-residue diet for 2 days before operation.

The variations in antibiotic bowel preparations provided an opportunity to study the effect of these different procedures on anastomotic and wound complications. Neomycin and Terramycin were significantly more effective than other preparations in patients undergoing extrarectal anastomoses. The use of parenteral antibiotics had no great impact on the incidence of either wound or anastomotic complications.

The postoperative complications of a nontechnical type are detailed in Table 9. A colostomy was employed in 42 patients in this series. All 23 patients who had complete colonic obstruction underwent proximal diverting colostomy preoperatively. An additional 15 patients required a diverting colostomy to protect the anastomosis. In spite of this, 2 of the 38 patients experienced anastomotic fecal fistula. Four additional patients underwent diversion of the fecal stream for postoperative anastomotic dehiscence.

TABLE 5. *Dukes' Classification*

Class.	Low anterior resection (556)	Anterior resection (346)
A	36 (6.5%)	26 (7.5%)
B_1	195 (35.1%)	115 (33.2%)
B_2	172 (30.9%)	112 (32.4%)
C_1	31 (5.6%)	15 (4.3%)
C_2	122 (21.9%)	78 (22.5%)

Differences between operative groups are not significant.

TABLE 6. *Involvement of Adjacent Organs*

Area of involvement	Low anterior resection (556)	Anterior resection (346)
Bladder	15 (2.7%)	8 (2.3%)
Small intestine	8 (1.4%)	7 (2.0%)
Left peritoneal wall or local perforation	23 (4.1%)	12 (3.5%)
No involvement	510 (91.7%)	319 (92.2%)

Differences between operative groups are not significant.

TABLE 7. *Operative Mortality*

Operation	No. of patients	No. of deaths	%
Low anterior resection	556	11	2.0
Anterior resection	346	6	1.7

Differences between operative groups are not significant.

Survival. The actuarial 5-year survival rate for the entire series was 72%, and for patients at risk 10 years it was 55%. There was no significant difference in the overall survival between the group of 346 patients undergoing anterior resection and the group of 556 treated by low anterior resection (Table 10).

As is usually the case, patients with involvement of the colonic wall no deeper than the submucosa (Dukes' type A) had an excellent survival rate, 88% at 5 years (Table 11). Invasion into the muscularis without lymph node involvement (Dukes' B_1) produced a 5-year survival rate of 85%. Patients with complete penetration of the bowel wall (Dukes' B_2) had a 5-year survival rate of 71%. Metastatic involvement of regional lymph nodes was associated with a decrease in the 5-year survival rate to 70% when the muscularis was penetrated (Dukes' C_1) and 47% when the full thickness of the bowel wall became involved (Dukes' C_2). The results with 10-year survival for both anterior resection and low anterior resection are summarized in Table 11. Survival according to the level of resection can be found in Table 12. These data are also provided with the variable of the Dukes classification included (Table 13).

Of interest were the survival data expressed according to the number of lymph nodes involved (Table 14). Of the 902 patients, 656 did not have lymphatic dissemination. The 5-year survival rate was 79%. This rate decreased progressively as more lymph nodes became involved until those patients who had 4 or more lymph nodes containing tumor had a survival rate of 30%. The data are also similar when the cases are separated into anterior resection and low anterior resection groups.

TABLE 8. *Causes of Death and Associated Major Complications*

	Low anterior resection	Anterior resection
Direct cause of death		
Congestive heart failure	5	4
Myocardial infarction	2	0
Cerebrovascular accident	0	1
Pulmonary failure	3	1
Ruptured abdominal aortic aneurysm	1	0
Total*	11	6
Associated major operative complications		
Anastomotic leakage	4	2
Fecal fistula	3	0
Total*	7	2

* Differences between operative groups (total) are not significant.

TABLE 9. *Postoperative Complications (Nontechnical)*

Complication	Per Cent (of 902)
Urinary tract infection	3.8
Prolonged ileus	3.9
Atelectasis	2.8
Thrombophlebitis	2.1
Other	3.3

Pathologic correlations were also derived concerning survival in relation to the length of normal colon present distal to the lower border of the tumor. This measurement was made from the fresh specimen in the pathology laboratory. Table 15 reveals that there is no correlation with survival if the length of the distal margin of resection is the sole criterion on which this judgment is based.

Recurrence. Recurrence after the treatment of colonic carcinoma by anterior resection or low anterior resection is a major concern. Among 346 patients treated by anterior resection, disseminated metastases developed in the liver of 63 patients and in the lungs of 19 patients. Similarly, when low anterior resection was the initial therapy, 94 of 556 patients experienced liver metastases, and 38 patients were found to have pulmonary metastases. Most of the patients in both groups with metastatic pulmonary lesions also had involvement of the liver.

More important to the evaluation of the operations themselves was the incidence of local recurrence, as this represents a true surgical failure. These types of recurrence were diagnosed by operation or autopsy when possible. However, in most of these patients, a clinical evaluation by means of physical examination and proctosigmoidoscopy was the method of detection. Anastomotic recurrence was considered to be present whenever a lesion was detected within 2 cm of the anastomosis and biopsy was obtained with the sigmoidoscope. Perirectal and pelvic recurrences were recorded whenever the examiner felt that, on examination intraoperatively, abdominally, or rectally, the perirectal or pelvic areas (or both) were involved with tumor.

Of the 556 patients undergoing low anterior resection,

TABLE 10. *Actuarial Survival*

	Survival, % (mean ± SD)	
Period of risk, yr	Low anterior resection (556)	Anterior resection (346)
5	71.1 ± 1.9	72.7 ± 2.4
10	54.7 ± 2.4	54.8 ± 3.0

Differences between operative groups are not significant.

TABLE 11. *Survival—Dukes' Classification*

	Survival, % (mean ± SD)					
	Low anterior resection			Anterior resection		
Class.	No. of patients	5 yr	10 yr	No. of patients	5 yr	10 yr
A	36	88.6 ± 5.4	67.5 ± 9.4	26	88.3 ± 6.4	79.4 ± 8.3
B_1	195	85.6 ± 2.5	69.2 ± 3.8	115	84.2 ± 3.4	62.9 ± 5.5
B_2	172	68.9 ± 3.6	47.0 ± 4.4	112	73.9 ± 4.2	53.0 ± 5.3
C_1	31	71.0 ± 8.2	61.7 ± 9.4	15	66.7 ± 12.2	49.3 ± 14.0
C_2	122	45.7 ± 4.5	36.0 ± 4.6	78	49.9 ± 5.7	38.1 ± 5.9

Differences between operative groups are not significant at 5 or 10 years.

6.8% (32 patients) were found to have had anastomotic recurrence. Of these 32 patients, 25 had perirectal or pelvic recurrence that precluded a second resection. In spite of the fact that the resection was performed with seemingly adequate margins (>5 cm), 2.8% of the patients undergoing anterior resection had anastomotic recurrence. Perirectal or pelvic recurrence (or both) was found in 5.7% of the group with anterior resection and 7.6% of the group undergoing low anterior resection.

The patients in whom there was local recurrence, including anastomotic recurrence, were classified according to the placement of the original tumor from the dentate line. These data are shown in Table 16. There was very little difference in the overall recurrence rate above the level of 8 cm to the dentate line. If the analysis includes this group the significance of the data, P approaches .05 but does not equal it.

In addition to location from the dentate line of the tumor, the length of the resected margin is an important parameter. The incidence of anastomotic recurrence and of perirectal and pelvic recurrences is shown in Table 17 related to the length of the distal resected margin. Again, there was no clear-cut advantage to the anterior resection. However, it must be noted that very few patients undergoing anterior resection had a distal resected margin of less than 5 cm, so that comparison of these data is less valuable.

Discussion

In order for two operations to be comparable, they should, ideally, have been undertaken on a similar group of patients for a similar disease. Because this analysis was performed in a retrospective manner and therefore was uncontrolled, it is impossible to achieve such comparability between those patients undergoing anterior resection for sigmoid carcinoma and those receiving low anterior resection for carcinoma of the rectosigmoid colon and of the rectum. Although dissimilar on the basis of several symptoms (Table 2), both groups were alike in the most important areas. Distribution of patients in both Dukes' and Broders' classifications were similar (Tables 4 and 5), and were the physical characteristics (Table 1). The groups were similar also with respect to duration of symptoms preoperatively and to symptoms known preoperatively to be usually associated with a poor survival rate (for example, obstruction).[11]

The use of low anterior resection for the treatment of carcinoma of the rectosigmoid and upper rectum has been criticized on the basis of three points: 1) an unacceptable operative complication rate,[3] 2) an unacceptable local recurrence rate,[16] and 3) a sacrifice in long-term survival to preserve bowel continuity.[19] By comparing the results of patient survival following the operation of low anterior resection with those after the standard anterior resection, several of these major problems can be investigated in a retrospective manner. The reasons for using these two operations, and their comparability, have already been established. The discussion can therefore conveniently be undertaken along the lines of the three major problems mentioned above.

Operative Complication Rate. Anastomotic dehiscence, partial or complete, continues to be a vexing clinical problem after all colonic anastomoses, especially those performed low in the pelvis in the extraperitoneal portion of the rectum. The incidence of this complication varies from a few per cent to a maximum of 70%.[3] The latter figure was obtained after intensive investigation with barium contrast roentgenography and is not representative of the overall incidence of clinically

TABLE 12. *Survival Related to Distance of Lesion From Dentate Line*

		Survival, % (mean ± SD)	
Distance, cm	No. of patients	5 yr	10 yr
0–9	145	66.7 ± 3.9	51.3 ± 4.6
10–15	290	71.3 ± 2.7	54.6 ± 3.3
16–19	121	75.9 ± 3.9	59.1 ± 4.9
≥20	346	72.7 ± 2.4	54.8 ± 3.0

Differences between groups are not significant for 5 or 10 years.

TABLE 13. *Survival* Related to Distance of Lesion From Dentate Line for Dukes' Classification*

Dukes' class. and period of risk		Distance from dentate line, cm			
		0 to 9	10 to 15	16 to 19	≥20
	No.	*5*	*18*	*13*	*26*
A†	5 yr	60.0 ± 21.9	100.0 ± 0.0	84.6 ± 10.0	88.3 ± 6.4
	10 yr	60.0 ± 21.9	92.3 ± 7.4	59.9 ± 14.1	79.4 ± 8.3
	No.	*90*	*203*	*74*	*227*
B†	5 yr	81.1 ± 4.1	75.7 ± 3.0	79.5 ± 4.7	79.1 ± 2.7
	10 yr	62.0 ± 5.7	57.2 ± 4.0	60.2 ± 6.3	58.1 ± 3.8
	No.	*50*	*69*	*34*	*93*
C‡	5 yr	41.3 ± 7.0	50.1 ± 6.0	64.7 ± 8.2	52.6 ± 5.2
	10 yr	34.7 ± 7.3	37.7 ± 6.3	57.3 ± 8.8	39.8 ± 5.5

* Expressed as % (mean ± SD).

† Differences between groups are not significant for 5 or 10 years.

‡ $P < .01$ for 16 to 19 cm vs. 0 to 9 cm at both 5 and 10 years. Otherwise differences are not significant for 5 or 10 years.

TABLE 14. *Survival Related to Lymph Node Involvement*

No. of positive lymph nodes	No. of patients	Survival, % (mean ± SD) 5 yr	Survival, % (mean ± SD) 10 yr
None	656	79.0 ± 1.6	59.4 ± 2.2
One	108	63.9 ± 4.2	47.8 ± 5.4
Two or three	73	53.4 ± 5.8	50.2 ± 5.9
Four or more	65	30.1 ± 5.7	21.5 ± 5.2

significant anastomotic problems. This complication rate has remained relatively constant at 7 to 9% since a previous report from this institution.[16] In addition to the morbidity produced by anastomotic leakage, this complication was an important factor in the ultimate death of 50% of the patients who died after operation. Therefore, the seriousness of this problem must be considered when evaluating a patient for this procedure intraoperatively.

Because all colonic anastomoses after sigmoid colon resection were performed intraperitoneally, these procedures were not fraught with many of the difficulties inherent in the construction of anastomoses deep in the pelvis. Blood supply is adequate, and the peritoneal lining provides more protection than does the large denuded area in the pelvis. Technically, placement of sutures should be less difficult as one proceeds cranially from the rectosigmoid to the sigmoid colon. Nevertheless, after anterior resection, anastomotic breakdown or fecal fistula occurred only slightly less often (6.6%) than it did after low anterior resection (9.0%). On the basis of the data presented, if the surgeon avoids the marginal anastomosis low in the pelvis, this major operative complication can be maintained at an acceptable rate. Because only 38 of 902 patients had the protection of a proximal diverting colostomy, it is impossible to assess accurately the importance of this procedure.

Recent data[9,17] have suggested that a combination of antibiotics together with mechanical bowel preparation can decrease technical postoperative complications in that both aerobic and anaerobic populations of bacteria are greatly diminished. The data in this study tended to support these conclusions. In addition, no data were obtained to support the use of parenteral antibiotics.

Incidence of Local Recurrence. Because of the anatomic configuration of the rectosigmoid and rectum, the local recurrence of colonic carcinoma remains a major problem in the treatment of carcinoma of the sigmoid colon, rectosigmoid colon and upper rectum. Much information is available demonstrating that a margin of normal colon of 2.5 cm in length[4,12] will be adequate in most cases. Because the lymphatic drainage from the rectum above 5 cm from the dentate line has been demonstrated to be upward along the superior hemorrhoidal system,[1,2] it is difficult to rationalize removal of the anus on this account for lesions in the upper rectum and above.

There is, in addition, mounting evidence that at least some of the recurrences in colonic anastomotic suture lines represent residual pelvic and perirectal disease that has simply invaded the rectum[6] in the area of the

TABLE 15. *Survival Related to Margin Between Tumor and Level of Resection*

Length of margin, cm	Low anterior resection: No. of patients	Low anterior resection: 5 yr	Low anterior resection: 10 yr	Anterior resection: No. patients	Anterior resection: 5 yr	Anterior resection: 10 yr
<2	39	78.4 ± 6.8	56.5 ± 9.9	5	80.0 ± 20.0	80.0 ± 20.0
2 to <3	111	74.8 ± 4.1	66.3 ± 4.8	17	82.4 ± 9.2	60.0 ± 13.0
3 to <4	155	70.8 ± 3.7	49.7 ± 4.8	44	81.8 ± 5.8	61.2 ± 8.4
4 to <5	95	60.9 ± 5.0	47.2 ± 5.4	36	74.3 ± 7.4	48.7 ± 9.5
≥5	156	73.6 ± 3.5	56.1 ± 4.4	244	70.0 ± 2.9	54.3 ± 3.5

Survival, % (mean ± SD)

Differences between operative groups are not significant at 5 or 10 years.

anastomosis. In support of this theory are the relatively high rates of pelvic recurrence after the combined abdominoperineal operation which vary from 9[8] to 25%[15]

When comparing the local recurrence rate after resection of the lesions in the sigmoid colon with that for lesions in the rectosigmoid and rectum, one finds that as one proceeds toward the dentate line the incidence of local recurrence does not increase significantly until the 8-cm level is reached. At this point the increase becomes only marginally significant (Table 16). Also, it must be noted that in the case of sigmoid lesions, in spite of the fact that wide segments of colon and lymphatic drainage were removed in each case, it was impossible to prevent totally any anastomotic and local recurrences.

The other important factor concerns the number of recurrences associated with the distance from the lower margin of the tumor to the resected margin as measured by the pathologist. As demonstrated by both survival data and the incidence of local recurrence, the patients undergoing the operation of anterior resection did not demonstrate a clear advantage in survival over those treated by low anterior resection. In addition, wide tumor-free margins did not influence either survival (Table 15) or the incidence of local recurrence (Table 17). Certainly one should strive to obtain as great a tumor-free margin as possible. However, the needless sacrifice of the anal sphincters need not be undertaken to achieve this goal.

Survival. Obviously, the ultimate survival rate is the most important criterion by which the results of a surgical procedure are judged. Much information is already available from this institution[5,18] and from others[3,5,10] which documents the nearly equal survival rates after curative resection of the upper rectum and rectosigmoid colon by the Miles procedure and after low anterior resection. Even though all palliative procedures were eliminated from this study, the actuarial 5-year survival rate of 72% and the 10-year survival rate of 55% are somewhat better than expected. The most likely explanation for this result is the fact that 73% of the lesions were Dukes' types A and B. This distribution among Dukes' A, B, and C lesions was the same for lesions above or below the 20-cm mark. Survival rates after anterior resection and low anterior resection were nearly identical. It is difficult to believe that this would be true if low anterior resection were an inherently poor cancer operation.

TABLE 16. *Incidence of Local Recurrence*

Distance of original tumor from dentate line, cm	No. of patients	Recurrences, no. (%)		
		Anastomotic	Perirectal and pelvic	Total
0–7	45	4 (8.9)	8 (17.8)	10 (22.2)
8–9	100	8 (8.0)	7 (7.0)	9 (9.0)
10–11	116	8 (6.9)	10 (8.6)	12 (10.3)
12–13	89	6 (6.7)	7 (7.9)	8 (9.0)
14–15	85	0 (0)	5 (5.9)	6 (7.1)
16–17	61	4 (6.6)	5 (8.2)	7 (11.5)
18–19	60	2 (3.3)	2 (3.3)	4 (6.7)
<20	556	32 (5.8)	44 (7.9)	56 (10.1)
≥20	346	10 (2.9)	20 (5.8)	25 (7.2)
Total	902	42	64	81

P approaches .05 when comparing anastomotic recurrences of lesion at <20 cm and ≥20. Otherwise differences are not significant.

TABLE 17. *Anastomotic Recurrence Related to Margin Between Tumor and Level of Resection*

Length of margin, cm	Recurrences, no.			
	No. of patients	Low anterior resection	No. of patients	Anterior resection
0 to <2	39	3	5	0
2 to <3	111	6	17	0
3 to <4	155	7	44	0
4 to <5	95	8	36	1
≥5	156	8	244	9
Pelvic and Perirectal Recurrence and Margin of Resection				
0 to <2	39	4	5	0
2 to <3	111	11	17	0
3 to <4	155	9	44	0
4 to <5	95	8	36	1
≥5	156	12	244	19

Differences between groups are not significant.

Conclusions

By analyzing the end results of the treatment of patients by anterior resection with those following low anterior resection, the criteria by which successful cancer operations are judged can be observed. On the basis of the data produced, low anterior resection was performed on a par with anterior resection on the basis of survival, operative mortality, and incidence of local recurrence. This in no way mean that a low anterior resection should be undertaken for every lesion in which it might be physically possible. Instead, the surgeon must evaluate all of the factors and variables discussed here in light of the presentation of the individual patient. Only in this way can the operation be effectively applied with safety to the greatest number of patients.

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DISCUSSION

DR. GEORGE L. JORDAN, JR. (Houston): Dr. Beahrs very kindly sent this paper to me for review, and as indicated on his slides, many of them having so many figures, he has a tremendous amount of data which will be extremely important, and worth your considered study.

The mortality rate which he reported is truly remarkable, I think, in such a large group of patients. I don't think it has been excelled in any other report that I have read.

A significant factor in the long-term survival rate, however, is the fact that only one third of the patients in this group had lymph node involvement at the time of surgery; and thus these were patients operated upon very early in the course of their disease. Most of us, unfortunately, don't see so many patients with such early disease.

I would like to comment on the limited resection done, as far as the distal resection is concerned. Low anterior resection is not done by many surgeons, because it is believed that a sufficient length of bowel distal to the disease cannot be resected. In this group of patients there were 145 tumors resected that were less than 9 cm from the dentate line. Despite that there is this excellent five-year survival, and an excellent mortality rate, indicating that spread of the disease distally is usually quite limited, and thus relatively limited distal resection can be accomplished.

He did not indicate—and I wish he would comment in his closing remarks—how much proximal resection was done, because many surgeons believe that the more we take out, the better our results will be, and this paper tends to present the opposite view.

I would like to ask Dr. Beahrs about his opinion of the no-touch technique. In performing a low anterior resection, the no-touch technique, as I understand it, is virtually impossible. One must manipulate the tumor before the bowel can be ligated proximally and distally, and if one is only resecting 2 cm distal, one can't ligate proximal to your point of resection.

So I would like to know whether or not the no-touch technique was used in the sigmoid resections, what he thinks about it as far as the low anterior resection is concerned, and whether or not he believes that this is a factor of significance in our consideration of the treatment of carcinoma of the colon.

And lastly I would like to ask him about the incidence of leakage. His incidence of leakage, I would say, is very similar to that which most others have reported; and yet he reports an extremely low mortality rate, and an extremely low incidence of the requirement of colostomy in treatment of anastomotic leakages. In the paper I think he has somewhere around 72 or 73 patients having anastomotic leakages, only four of whom required colostomy in their treatment.

Do you drain all of these now? Do you drain the anterior resections? I know you drain the low anterior resections, but do you drain the sigmoid resections too? Many leaks occurred in the anterior resections as well as in the low anterior resections. If not, how do you recognize these leakages, and how do you treat them?

DR. ISIDORE COHN (New Orleans): Drs. Wilson and Beahrs allowed me to see an early draft of their paper, where there are tremendous numbers of figures which they did not have a chance to present, but which give considerable validity to the points they have tried to make.

Everyone should be aware of the good results they have reported which many institutions, including ours, will not be able to duplicate.

(Slide) These figures are from a 1948 to 1968 study at Charity Hospital of 2313 histologically proven cases of cancer of the colon. One line of the chart is the general population survival figure, as determined from life table studies, and another shows what happens to patients with cancer of the colon. As you see, our five- and our ten-year survival figures are nothing at all like those reported tonight.

(Slide) Here the results are based upon the kind of resection the surgeon thinks he does. Even with the so-called curative resection, we have not achieved the same survival as reported tonight. This is to call your attention to differences in different institutions and to warn you that you should not think that you will duplicate the results that have been presented to you tonight.

(Slide) This is one study of a totally different type. We were interested in the incidence of recurrence following various types of anastomoses. This is a very special series of patients, all of whom had histologically proven disease, and all of whom came back to the hospital and were autopsied in the hospital at some date sufficiently long after their original operation so that one could get some idea of whether or not recurrence was likely to occur.

In our hands, there is a noticeable difference in the incidence of recurrence following an abdominoperineal or an anterior resection.

We have been somewhat frightened of the anterior resection because of this factor, if for no other reason.

If you are going to do an anterior resection, and you don't have sufficient technical knowledge of how to do it exactly the way Dr. Beahrs has pointed out tonight, you should be very much aware of the possibility of a recurrence at your anastomosis.

DR. A. HAMBLIN LETTON (Atlanta): What worries so many of us is the fact that when we see a patient come into our office, or our clinic, with cancer of the colon, we know that there's less than a 50/50 chance that he will not be cured. This is a tremendous burden on us, and it takes a tremendous toll on the people of our country.

The mortality rate has been about the same for a long time. A few years ago, Barton McSwain reported to this organization that he had seen some change in the delay time that patients have had, the delay time in physicians, but as I recall, in the last report he made, there was some three months' delay from the time the patient first had symptoms until they came to see the physician, and there was about a 2.8-month delay from the time the doctor first saw the patient till something was done.

Now, this is almost five months that everybody thought this poor fellow had the piles, instead of doing something about it.

Now, for a long time we have talked about doing proctosigmoidoscopy, to try to find these malignancies earlier, but this, for some reason, is not a very habit forming examination, and people don't much like it, and we doctors don't like it either. And we have to find something else.

When I was Chairman of the Executive Committee of the Cancer Society, Gold brought forth the CEA, and we thought this was going to be a great bonanza in trying to find carcinoma of the colon earlier. But lo! it hasn't been. We're still up against this matter of trying to find some way to screen people to find malignancies of the colon at an earlier stage, so that they may be cured.

Our best hope at present is through the Hemocult, a little piece of paper I'm sure all of you are familiar with. The patient puts a little bit of stool on it, and sends it in to you, and you put some reagent on it, and it turns it blue.

Admittedly, it takes a lot of blood to cause this thing, but still, it's a very fine screening process. At least, it's the best we have today.

I would hope that you and your colleagues would start using the Hemocult with your patients, and try to find these bleeding people earlier.

There's one other thing that I think that we should talk about. We have had so many people come to us and say: My doctor took my cancer out, but he left me with this stinking colostomy. It's your and my duty to take care of these people, to be sure that they are returned to a good life.

It's down in St. Matthew: "What does it profiteth a man, if he gains the whole world and loses his soul?" And what does it profiteth a man if you cure him of cancer of the colon, and you leave him with a colostomy that is abhorrent to his family and to his friends? We must teach him to take care of that.

DR. DOUGLAS H. RIDDELL (Nashville): It appears one thing that all of us are probably trying to do here tonight is to resect a lesion in the rectosigmoid region which is lower than we would have resected 20 years ago. I believe that's a true statement, with end-to-end anastomosis being accomplished from the technical standpoint.

In a private group of patients in a surgical group, of which I'm a member, we have had just fewer than 300 such cases. One of our partners trained at Memorial Hospital in New York, which was a pioneer in the lower anterior resection, has stimulated me as a senior partner in doing as low a resection as possible where a curative outlook seems to be reasonable.

One possibly archaic method that may be used and we use it quite often, is a very low anterior resection, below the pelvic floor with a one-layer silk anastomosis. I protect the one-layer anastomosis *not* with a colostomy, which makes more morbidity and makes for a closure of a colostomy but with a "tube cecostomy" with a Pezzer catheter which can be removed in 2 or 2½ weeks. We begin in 48 hours to irrigate the Pezzer catheter into the bedside bag, that is a good indication that peristalsis has resumed. I am convinced that it is a protective procedure that does not increase the morbidity of the patients, and I believe that it decreases the mortality.

We have not had to drain a pelvic abscess in these people. We have had one suture line dehiscence with insertion of a Penrose drain from below but not an abscess. We have had one death from a pulmonary embolism, and one from coronary thrombosis.

This is just a suggestion of the old-time procedure of a "tube cecostomy", where the tube is always brought into apposition with the parietal peritoneium. Whether it's a gastrostomy or "tube cecomy", always make it in close apposition with it sutured to the perietal peritoneum.

DR. OLIVER H. BEAHRS (Closing discussion): One of the important things that should come out of the discussion of these two papers is the fact that cancer should be properly staged as to the extent of disease. The American Joint Committee for Cancer Staging and End Results Reporting is working on programs of cancer classification and staging and if used, we more likely will be presenting data on similar groups of cases so statistics most likely will be comparable.

Several methods of staging cancer of the colon are available presently. One is by the degree of differentiation, as proposed by Broders, and the other is the Duke's classification as to the extent of disease. If we stage cancer, and talk about like groups, Duke's C versus Duke's C, irrespective of where the cancer population might come from, our figures should be meaningful. Too often we group all cancers together, and this makes the total group look worse than the favorable patients within the group versus the unfavorable patients within the group or the groups as a whole.

Our mortality figures are based on hospital mortality-deaths while the patients are hospitalized following surgery. The usual period of hospitalization is 10 to 14 days. Our mortality figures than are not based on a certain period of time or on death following hospital dismissal.

In doing an anterior resection, we attempt to get as far below the lesion as we can conveniently and still reestablish intestinal continuity, if it seems feasible based on all known factors regarding the cancer. As far as the resection proximal to the cancer we resect as much colon as can be conveniently removed and still have sufficient bowel to reach rectum without tension on the anastomosis. Left hemicolectomy, or freeing the splenic flexure, rarely is necessary to have sufficient bowel to reach the remaining rectum.

Dr. Turnbull has popularized the no-touch technique, which is important in that it emphasizes to all of us that we should treat cancer with care and gently. It's impossible, as Dr. Jordan mentioned, to treat the cancers of the upper rectum and rectosigmoid by a no-touch technique. One has to touch these lesions; but we should touch them gently and carefully. We can do this with minimum trauma to the lesion by approaching the dissection adjacent to the bowel, creating the tension on the mesentery, or adjacent tissues, not on the bowel itself and certainly not through the tumor itself.

Drainage is a controversial subject, but I would argue very strongly in favor of drainage when is dealing with an intestinal anastomosis that is extraperitoneal. But suction drainage, serum, hematoma, or exudate that might collect in a violated retroperitoneal space can be aspirated. Viable surfaces will be approximated and more likely will seal together preventing the complications of abscess formation and leakage from an anastomosis.

Don't reperitonealize the pelvic floor following an anterior resection or a low anterior resection. If reperitonealized a retroperitoneal space which has been violated is isolated. There is no better environment for infection if it should occur. Peritoneal surfaces can better handle this complication.

With suction drainage, which I think is as important in colon surgery as the use of antibiotics today, you can eliminate serum, hematoma, and exudate. But if you do get a dehiscence, or a partial dehiscence with fecal drainage, you aspirate it out your drain site. You know that you have a fecal drainage. With suction drainage if dehiscence of the anastomosis does occur a fecal fistula will develop but will almost always heal in a short period of time without mortality. Without drains in place, risk of severe complication and death is present from abscess and fecal peritonitis.

Recurrence of cancer will be at the anastomosis. When we compared low anterior resections versus a Miles operation, the figures are this: 55% five-year survivals with a Miles and 51% low anterior resections in like patients. Interpreting these figures means that the prognosis is 4% less for anterior resections, due in some cases undoubtedly to recurrence at the anastomosis. Had a combined abdominal perineal resection been done these patients may have survived. However, in doing a combined abdominal perineal resection in all patients, all would have lost anal function.

In this study recurrence of the cancer at or near the anastomosis was most likely due to the extension of the cancer into the perirectal tissues at the time of surgical treatment rather than related to the type of surgical procedure done. In other words, the recurrence, in fact, is a persistence of the cancer, or lack of total removal of the lesion irrespective of whether an anterior resection or combined abdominal perineal resection is done.

Dr. Letton has made an important point regarding enterostomal care. The surgeon is responsible to see to it that the patient gets instruction regarding stomal care, either providing it himself or by an enterostomal therapist or nurse specialist if available.

Dr. Riddell brought up the question of one-layer anastomosis. An anastomosis can be done by several methods. However, to me an anatomic anastomosis is best. This means careful approximation of the muscularis, or the muscularis and peritoneum by a second row of interrupted silk sutures.

As far as the tube cecostomy is concerned, I have no objection to its use. If decompression is really necessary a complimentary proximal colostomy is best done. With negative suction drainage and a satisfactory anastomosis serious complications are very infrequent.

Long-Term Ventilatory Support by Diaphragm Pacing in Quadriplegia

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Thirty-seven quadriplegic patients with respiratory paralysis were treated by electrical stimulation of the phrenic nerves to pace the diaphragm. Full-time ventilatory support by diaphragm pacing was accomplished in 13 patients. At least half-time support was achieved in 10 others. There were two deaths unrelated to pacing in these two groups. Fourteen patients could not be paced satisfactorily, and 8 of these patients died, most of them from respiratory infections. The average time the 13 patients on total ventilatory support have had bilateral diaphragm pacemakers is 26 months. The longest is 60 months. Many of these patients are out of the hospital and several are in school or working. Injury to the phrenic nerves either by the initial trauma to the cervical cord or during operation for implantation of the nerve cuff was the most significant complication. Nerve damage from prolonged electrical stimulation has not been a problem thus far. A description of the pacemaker, the technique of its implantation, and the pacing schedule are reported.

IT HAS NOW BEEN nearly 5 years since total support of ventilation was first accomplished in a quadriplegic patient by means of bilateral, programmed electrical stimulation of the phrenic nerves (diaphragm pacing) (3). That patient continues to do well, unaided by mechanical respiratory support. He has been living at home since May, 1971, and is gainfully employed. Diaphragm pacing has subsequently been applied with varying success to 36 other patients with respiratory paralysis accompanying quadriplegia. Nine of these patients were treated in our institution, the remainder in a number of other institutions. As far as we know, this is the total experience with diaphragm pacing in quadriplegic patients.

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The Clinical Series

The collected series of 37 patients with quadriplegia who could be paced was reviewed. There were 24 males and 13 females whose ages ranged from 4 to 71 years. The largest proportion of cases were young adults, in the age group of 15 to 30 (Fig. 1). Quadriplegia was caused by violent injury to the spinal cord in all but 3 patients, of whom two developed complete paralysis from ischemia of the cord following surgical procedures attempting to relieve osseous compression of the cord and one developed incomplete paralysis as a consequence of syringomyelia. The last was the only instance of incomplete quadriplegia in the series (Table 1). In 27 patients the lesion involved predominantly the C1-C2 segments of the cord, in the other 10 patients the C3-C5 segments.

The cuff electrode and the receiver were implanted two months to 11 years after the initial injury. In the patients who had normal nerves positive pressure ventilation could be omitted for at least part of the time within one month after pacing was started. Delay of full-time support by pacing was sometimes the result of emotional instability, especially prevalent in the children.

Full-time pacing was accomplished in 13 patients. These patients used no other form of ventilatory support and had no ventilation except what they could achieve with their neck muscles. In 10 other patients ventilation was provided by pacing at least 50% of the time. Two of these were paced for 18 hours daily and did not require

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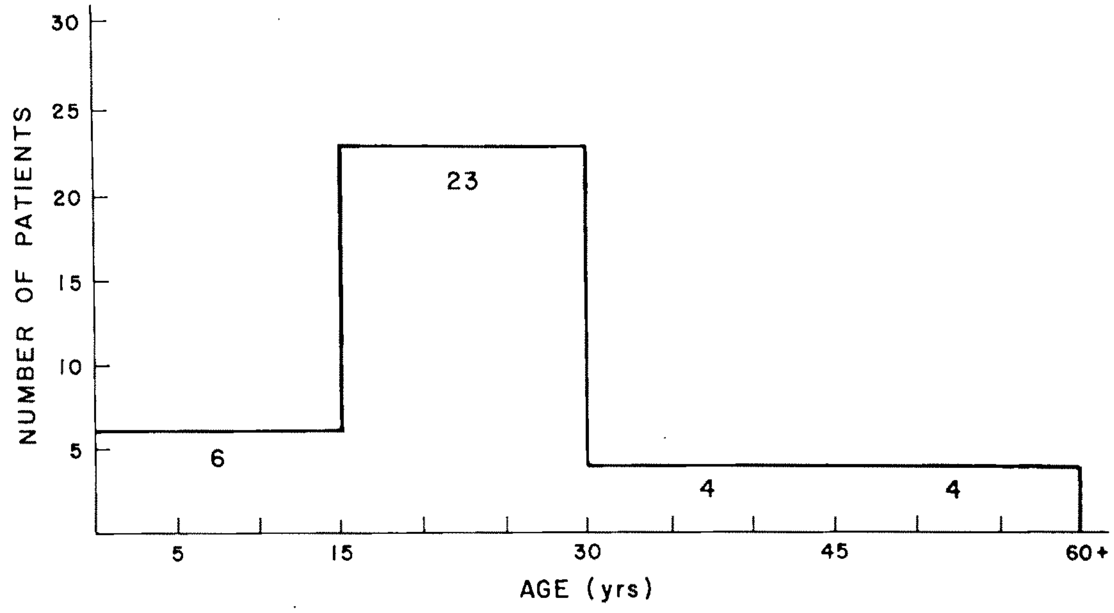

FIG. 1. Age distribution in quadriplegic patients who have achieved partial or complete ventilatory support by diaphragm pacing. Twenty-three of the 37 patients fall within the age group of 15 to 30 years.

positive pressure breathing; one, the patient with syringomyelia, was able to support her respirations voluntarily for 6 hours daily, and the other patient, who had a transection at C2, used a pneumobelt while sitting for 6 hours daily. Total ventilatory support was thus provided by diaphragm pacing for 50 to 100% of the time in 23 patients, 62% of the series. Two of these patients (9%) have died; one, who was on full-time pacing, died as a result of meningitis secondary to a sacral decubitus and the other died in his sleep, presumably as a result of respiratory arrest, 4 months after resumption of voluntary respiration and discontinuation of pacing.

In the remaining 14 patients in the series ventilatory support for as much as 50% of the day could not be achieved. Eight of these have died. Most of the deaths resulted from respiratory tract complications (Tables 2 and 7).

The average time elapsed since implantation of the pacemaker in the 13 patients whose ventilation was supported totally by diaphragm pacing is 26 months; the longest period of continuous support is nearly 5 years (Fig. 2). The time of the beginning of full support by diaphragm pacing after implantation of both phrenic nerve stimulators was usually 2 to 4 months but could not definitely be ascertained in all cases.

Failure to pace or ineffective pacing resulting from malfunction of a pacemaker component was usually due to shorting out of electronic components in the receiver because of flooding, or to a breakage of the antenna connector. No case of failure due to breakage of an electrode was reported in the series (Table 3).

Injury to one or to both phrenic nerves was the major cause of failure of the attempt to support ventilation. Four nerves showed no response, i.e., diaphragm contraction, to direct stimulation at operation and it must be presumed they were destroyed by the initial trauma. In 11 instances absence or weakness of the response to neural stimulation was attributed to iatrogenic trauma during application of the cuff electrode to the nerve. In a number of other cases there was less than the expected response and in these the nerve may either have been damaged by the initial injury or by operative manipulation. Partial or complete recovery of a nerve injured at operation was seen in two cases 12 and 16 months postoperatively.

Infection of the implanted unit occurred in 5 cases. In one case the infection involved only the site of the electrode junction. The junction point was exposed, thoroughly cleansed with povidone iodine and reim-

TABLE 1. *Causes of Quadriplegia*

Automobile or motorcycle accident	16
Sports injury	14
Gun shot wound	4
Disease (syringomyelia)	1
Postoperative ischemia of cord	2
Total	37

TABLE 2. *Results*

	Patients	Deaths
Full time pacing	13	1
Part time pacing		
>50%	10	1
<50%	14	8
Total	37	10

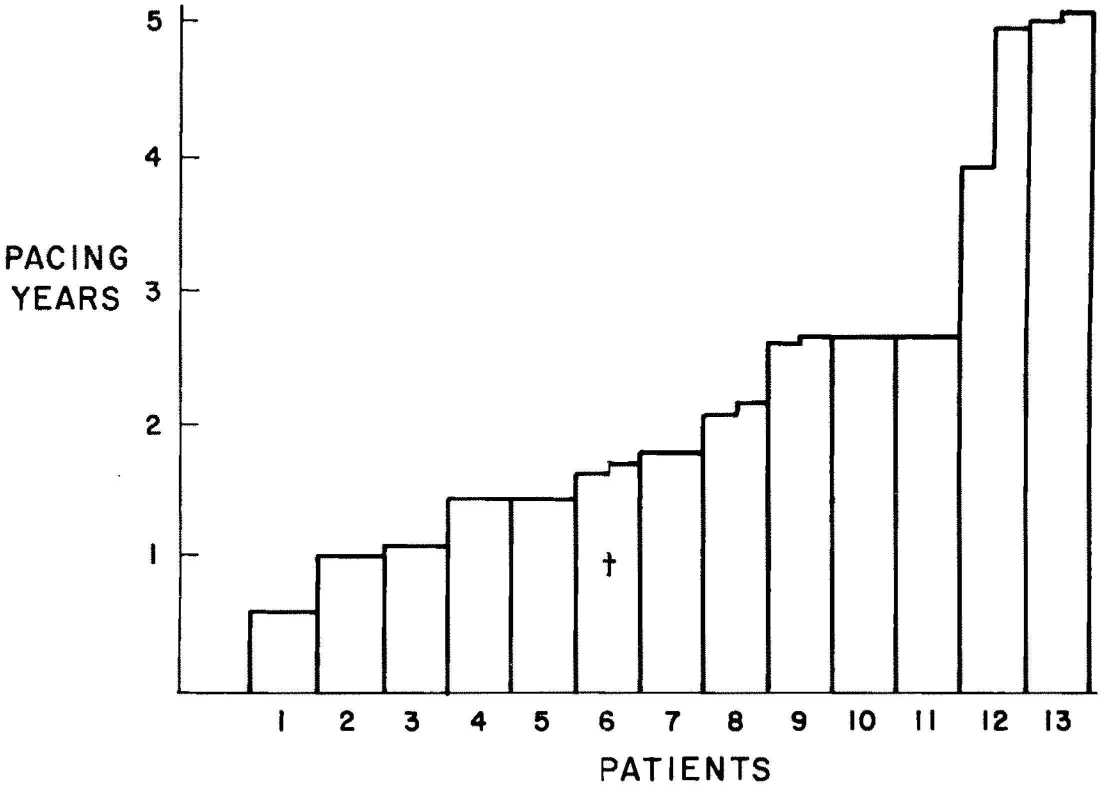

FIG. 2. Time elapsed since implantation of bilateral phrenic nerve stimulators for pacing the diaphragm. There was one death 20 months postoperatively due to meningitis complicating sacral decubitus ulceration.

planted in an uncontaminated subcutaneous pocket. Prior to its closure the wound was thoroughly irrigated with antibiotics, then systemic antibiotic coverage given for several weeks. In cases where the infection involved the electrode cuff site, removal of the cuff was necessary in order to control the infection.

The effects of long-term electrical stimulation on neural function could be evaluated only in the 9 patients treated in our clinic and not in all those in the collected series. Pacing provided total ventilatory support for 4, and support for at least 50% of the time for 3. The other two could not be paced adequately; one of these died, as did one who was fully supported by pacing but developed meningitis as previously noted. The adequacy of pacing was assessed periodically by analysis of arterial blood gases, studies of tidal volume, measurements of diaphragmatic excursions and determination of the current required to achieve minimal (threshold) and maximal contraction of the diaphragm.

The 7 patients who were paced 50 to 100% of the time showed nearly normal arterial blood gases when these were measured at the beginning and end of any 12-hour pacing period. Hyperventilation was common as evidenced by the somewhat lower than normal levels of CO_2 (Table 4).

The minute volumes in the patients totally supported by pacing were usually in the normal range, 5 to 10 liters per minute (Tables 4 and 5). At the start of treatment they were sometimes lower than normal but increased with daily pacing.

The threshold level noted initially at operation was invariably lower than levels measured subsequently. There was a rise for about 6 months from the start of pacing and then a slow fall over the next few years. In the longest-paced quadriplegic, thresholds at operation and after 5 years of pacing were 1.5 mA and 3.04 mA respectively on the right side, and 0.7 mA and 1.02 mA respectively on the left side (Fig. 3).

Diaphragmatic excursions during pacing were observed fluoroscopically and a ciné record made. When the nerve being stimulated was undamaged and the patient was lying supine, a descent of the diaphragm of 6 to 10 cm was the usual finding. Restriction or absence of movement was evidence of a damaged nerve.

Postmortem examination of the phrenic nerves of two quadriplegic patients was made by Drs. J. Kim and E. Manuelides.* Microscopic examination of the nerves from one of these patients showed focal demyelination and macrophages at the site of the electrode cuff. The patient, a 36-year-old man with a C2-C3 transection, had been paced for less than three months when he died suddenly. His ventilatory exchange on pacing had been

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* This material together with the results of microscopic examination of the stimulated nerves of four other patients with Ondine's Curse is being prepared for a detailed report by Dr. Kim and associates.

TABLE 3. *Complications*

Operative	
Probable nerve injury	11
Infection	5
Pacemaker	
Receiver failure	11
Antenna connector breakage	6

Table 4. Ventilatory Studies

Side paced	$\dot{V}E$ (liters/min)	P_{CO_2} (mm Hg)	P_{O_2} (mm Hg)
Right			
At start	5.8	24	108
After 12°	5.9	25	98
Left			
At start	6.2	27	103
After 12°	5.5	27	101

Data on Patient K. deS., a 19-year-old quadriplegic woman, are given. The dates of phrenic nerve implantation are as follows: left side, Jan. 18, 1971; right side, Jan. 10, 1972. This study was performed in April, 1973. (After Glenn et al.: J Thorac Cardiovasc Surg 66:505, 1973).

Addendum: For more than 3 years, this patient has followed a schedule in which pacing of the sides was alternated at each breath for 14 to 16 hours daily and was of both sides simultaneously, to enable sitting, for 8 to 10 hours daily. On this schedule, ventilatory studies were repeated in December 1975: $\dot{V}E$, 4.61 liters/min (average of 5 measurements); P_{CO_2}, 28.8 mm Hg; P_{O_2}, 114 mm Hg; the current required to produce minimal contractions (threshold) had decreased in the interval to less than 1.5 mA on both sides.

poor from the day of operation and full-time pacing was never achieved. The second patient, a 29-year-old man with a C2 transection, achieved full-time support with no difficulty and pacing of each side gave a minute volume of 10 to 14 liters. He died of meningitis 20 months from the start of pacing. Careful examination of both nerves failed to reveal any significant abnormality.

Materials

The Diaphragm Pacemaker

The radiofrequency (RF) unit used for pacing all patients in this collected series was developed at Yale in the early 1960's and as modified since then has been described.[2,4] Briefly, it consists of an external battery-powered transmitter, an antenna placed on the skin, a radio receiver embedded subcutaneously beneath the antenna, and platinum electrodes which surround and conduct current to the phrenic nerve. The transmitter creates a series of 33 radiofrequency pulses of short duration spaced by intervals of 37 msec. This series of pulses may be adjusted (in the transmitter) so that the first pulse in the series matches the threshold to stimulation and the 33rd pulse provides optimal diaphragmatic motion. Current delivered by the receiver to the nerve increases about 7 µamp per µsec of pulse duration. Exact conversion characteristics of the receiver can be calibrated prior to implantation. This design provides capability of generating current from 0 to 10 mA from a receiver with a constant current characteristic.[5] Threshhold currents are determined from the receiver calibration.

Application of this pacemaker to the 9 patients under our care and review of the total series have revealed to us certain points relative to the conduct of diaphragm pacing that bear emphasizing.

Battery Life. A fresh 9-volt alkaline battery will operate the pacemaker for about 40 hours. At the end of each 12-hour period of use the battery should be checked for the remaining charge by an instrument provided for this purpose; eight volts or more are necessary for safe pacing. Larger, rechargeable batteries (lead acid, such as a 12-volt motorcycle battery), carried separately in the patient's wheel chair or kept by the bedside, may be more convenient for certain patients.

Transmitter. The variable potentiometer regulating the current is fragile and must be turned carefully. Other adjustments on the transmitter (stimulus slope, pulse width, and respiratory rate) are manipulated only according to the manufacturer's instructions. No attempt should be made to increase the minute volume by increasing the rate beyond 17 per minute or the current beyond that which at fluoroscopy produces a maximal contraction.

Antenna. The connector between the antenna and the transmitter is especially vulnerable to rough handling; care must be exercised to line up the ends correctly when making connections. The antenna is held to the skin overlying the receiver with one or two strips of paper tape; this skin should be cleansed daily.

Receiver. The most common complication we have encountered with the unit during diaphragm pacing has been failure of the radio receiver. This has usually occurred during the first two years after implantation. Impending failure is most frequently heralded during pacing by a sharp pain over the electrode site in the neck or by erratic pacing. Occasionally pacing stops abruptly without warning. It is therefore essential that patients dependent upon pacing be provided with an alarm to summon help. Should confirmatory tests of electronic equipment indicate failure of the receiver, the latter must be

TABLE 5. *Ventilation During Diaphragm Pacing*

Date	Body position	Voluntary assistance	Minute volume l/min
1971	Reclining	no	8.4
		yes	11.4
1975	Reclining	no	8.7
		yes	11.5

Data given for J. C., age 38, following C1-C2 injury.

replaced immediately; stimulation of the opposite nerve will support the patient only 12 to 18 hours before nerve fatigue begins to impede ventilation. Provisions must *always* be made to return to endotracheal positive pressure ventilation in the event of pacemaker failure.

Electrodes. Malfunction of the cuff electrodes has not been a problem except from infection or from trauma during implantation, as described above.

Methods

Schedule for Operation

When damage to the spinal cord and resulting respiratory paralysis appear to be permanent, implantation of a pacemaker should be considered. Implantation is delayed at least two to three months after injury, however, to allow for a possible return of diaphragmatic function, as was seen in a few patients in the series several months or more following the cord injury, and allow time for the patient to become thoroughly acquainted with the use of positive pressure ventilation in the event of pacemaker failure. Respiration is provided in the meantime by positive pressure ventilation.

Viability of the Nerve

The primary requirement for successful pacing is viability of the phrenic nerves. This may be ascertained preoperatively by percutaneous stimulation of the nerves where they pass over the scalene muscles. The technique used by Sarnoff[8] is employed (Fig. 4). With practice the nerves can readily be located. A quick hiccup-like contraction of the diaphragm on the side of stimulation is evidence of the integrity of the nerve and if the contraction is vigorous most of the neurons are probably viable. Failure to obtain diaphragmatic contractions upon stimulation usually indicates non-viability but when in doubt one should explore the nerve directly. The surgeon exploring the nerve must be prepared to place an electrode upon it if he finds it viable. Assessment of neural function by studies of conduction time using percutaneous stimulation according to the technique of Davis[1] is advised in the preoperative period to provide a comparison after placement of the nerve in the cuff.[9]

Operative Techniques

Attachment of Cuff and Receiver

The technique for applying the cuff electrode and installing the radio receiver in the 9 Yale patients is that which we have used in our clinic since 1968. Briefly, it is as follows:

In the adult, under local anesthesia, a 4-inch transverse incision is made one inch above and parallel to the clavicle. The phrenic nerve is isolated where it crosses the scalenus anticus muscle and an electrode cuff is placed around it. Insulated wires connect the cuff to the radiofrequency receiver implanted in the subcutaneous tissue of the anterior chest wall. In the child under 12 years of

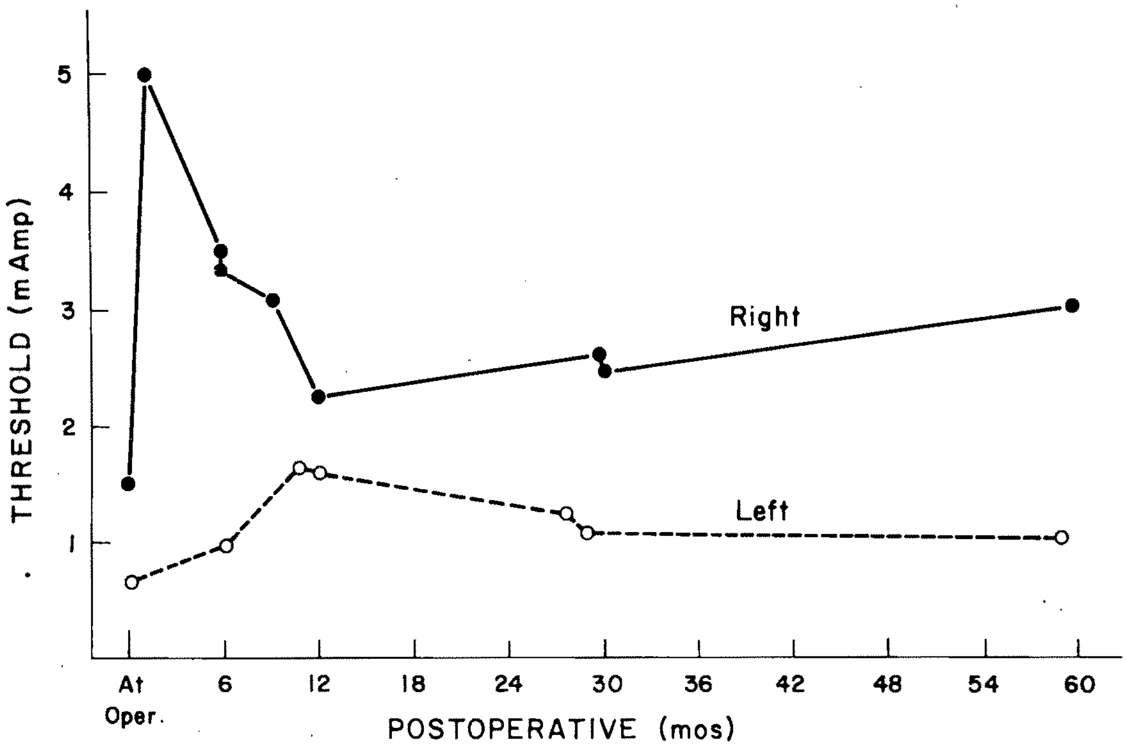

FIG. 3. Threshold to stimulation (minimum current required to produce diaphragmatic contractions) in a 38-year-old C1–C2 quadriplegic over a 5-year period. The current required to stimulate the right diaphragm soon after pacing was started was uniquely high but movement of the two sides of the diaphragm was the same.

age whose neck may be too short to accommodate the cuff, it can be placed at thoracotomy and at a site as far from the heart as is feasible in order to lessen the chance of stimulation-induced fibrillation.

Precautions with Cuff Application. Damage to the phrenic nerves during implantation of the electrode is the most serious complication and was apparently the cause of failure to pace in 11 nerves (16% of the nerves stimulated in the collected series). For this reason certain points in the technique of application[4] deserve reemphasis. 1) Sterilization of the *cuff electrode must be by autoclave only*; a residue on the cuff of ethylene oxide or chemicals ordinarily used for sterilization could severely injure the nerve. The receiver, which does not come in contact with the nerve, may be sterilized by ethylene oxide or in the autoclave; we prefer gas sterilization as it subjects the electronic components to less heat than does autoclaving. 2) The electrode-receiver assemblies, two of which are required in the quadriplegic for stimulating both phrenic nerves, are each implanted at a separate operation to provide time for meticulous dissection and to lessen the danger of infection. 3) Identification of the phrenic nerve where it passes over the scalene muscle is accomplished atraumatically with single stimulation of 1 to 10 volts. Of course, local anesthetic must not be instilled in the vicinity of the nerve. 4) Isolation of the nerve and placement of it within the cuff is carried out with utmost care and gentleness. The prescalene fascia is not removed from the nerve. Instead, parallel incisions about 15 mm long are made through the fascia two to three mm on both sides of the nerve, with care taken to preserve the perineural blood supply. With the nerve elevated slightly by a right-angled clamp or nerve hook, the posterior lip of the cuff (5 mm ID) is slipped behind the nerve; traction on a suture attached to the posterior lip and inserted behind the nerve will aid this. It is at this point that injury is most apt to be inflicted. The most common injury is impaling the nerve or perineural tissue on the tip of the platinum electrode as it is passed behind the nerve. Once the nerve is in place in the cuff it should lie loosely and have no angulation where it enters and leaves the cuff. 5) Cephalad orientation of the horn of the cuff, marked with a red thread, is important to insure stimulation of the nerve by the cathode electrode.

When a diaphragm responds at operation but fails to be paced at any time postoperatively iatrogenic injury is suspected. It is probably wise to remove the cuff in such cases and let the nerve recover, which may take 6 to 18 months. The cuff could then be reimplanted at thoracotomy at a point lower on the nerve. Removal of the cuff is not obligatory for recovery if the cause of the injury has been removed.

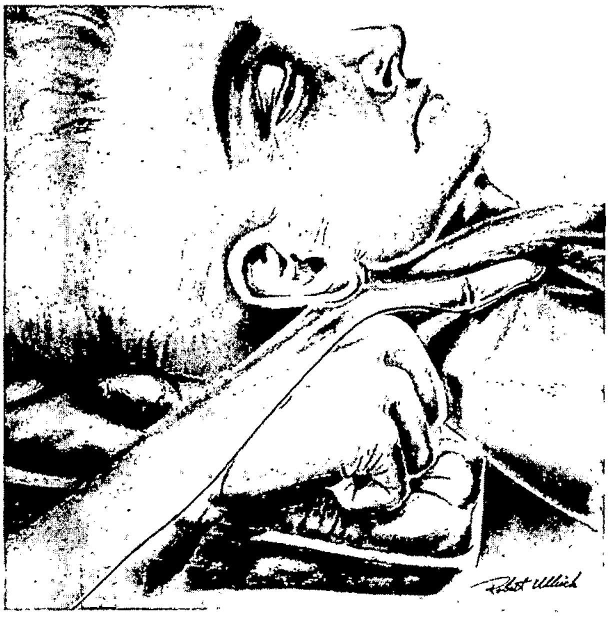

FIG. 4. Sarnoff's technique[8] for percutaneous location of the phrenic nerve in the neck. This procedure is used to determine viability of the nerve prior to cuff implantation and to obtain with the aid of skin electrodes in the 8th interspace the phrenic nerve conduction time.[1,9]

Implantation of Receiver. Following application of the cuff electrode to the phrenic nerve a second transverse incision, 3 to 4 inches long, is made at the costal margin in the mid or anterior axillary line to create a subcutaneous pocket which is then developed cephalad 3 to 4 inches deep. A third incision, two inches long, is made at the level of the fourth rib in the midclavicular line to provide access to the silastic-covered wires from the cuff electrode above and the receiver below. The wires from the receiver and from the cuff are brought towards each other within subcutaneous tunnels. Subcutaneous passage of the wires from the cuff electrode is facilitated by passing a plastic chest tube (#28F) through the third incision, then into the neck wound above and threading for a short distance the tip of the electrodes into the open end of the tube. When the tube is withdrawn through the incision the electrode wires, except for the terminal segments, remain in the tunnel and the ends become accessible externally for connecting to the ends of the receiver electrodes, passed subcutaneously from below in like manner. Following insertion of the radio receiver into its pocket, connections are made between the electrode wires of the receiver and cuff, with anodes and cathodes matched according to identifying red markers. The electrode wire connection is further secured with a monofilament synthetic ligature. The junction and any excess wire are implanted in a Teflon (0.5 mil thick) bag subcutaneously for easy accessibility should replacement become necessary. All incisions are closed and dead space obliterated with multiple interrupted sutures of plain

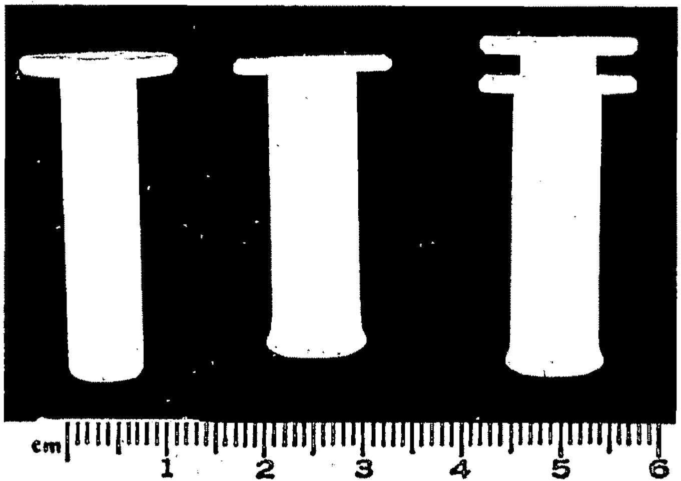

FIG. 5. Teflon tracheostomy button used to plug the tracheostomy stoma during diaphragm pacing (Quinton Instrument Co.).

catgut, with care not to incorporate the electrode wires in the sutures. The integrity of the system is checked by stimulation with a sterile antenna prior to closure of the wounds. Nerve-electrode contact is assured by flooding the neck wound with saline.

Pacing Schedule

To allow time for postoperative edema to subside, stimulation of the nerve is not begun for at least 12 days after implantation of the unit. If the stimulators have been implanted separately, as we advise, one side will be about two weeks behind the other on the pacing schedule. When pacing is begun the patient is fluoroscoped and the extent of diaphragm motion measured for future comparison.

The diaphragm in many quadriplegics is weakened from prolonged inactivity and must be conditioned through a gradual lengthening of the periods of stimulation. Generally, at the beginning, stimulation is done for 5 minutes of each hour. Tidal volumes are measured at the start and finish of each period of stimulation. If the tidal volume at the end of the period is 75% or more than at the beginning, the length of pacing can be increased. Usually we have increased it one to two minutes per hour per day until the diaphragm is being paced 30 minutes in each hour. The periods of pacing can then be lengthened by 5-minute per hour increments daily. Positive pressure ventilation is continued during this conditioning of the diaphragm or, if the minute volume is adequate (>5 l/min in adults), it can be discontinued during the periods of pacing. Usually diaphragm conditioning is done only during the waking hours, the respirator being used during sleeping. When one hour of pacing is reached with an adequately maintained minute volume a similar period of rest is scheduled. Pacing then is increased by 15-minute increments daily until 6 hours is reached. This is followed by a similar rest period. At this point it is usually possible to increase pacing up to 8-, 10- and 12-hour periods. When pacing on each side has been extended to 12 hours, while producing satisfactory minute volumes and normal arterial blood gases, the patient can be taken off the respirator completely. This weaning has usually taken from 2 to 3 months.

Sitting during pacing causes the minute volume to drop sharply. It can sometimes be raised by wearing an abdominal belt to elevate the diaphragm, which increases the effectiveness of pacing, and/or by pacing both sides simultaneously. An alternative is the use of a pneumobelt without pacing, a practice carried out by several patients in the series.

Once the maximal stimulation time has been established, several schedules for maintaining it have been adopted. To those patients who respond normally to stimulation of either side of the diaphragm, we recommend pacing each side alternately, 12 hours at a time. A few patients prefer to alternate pacing with each breath. Both sides of the diaphragm may be paced simultaneously for as long as 8 hours daily. When only one side can be paced, stimulation of the phrenic nerve for longer than 16 hours daily is not recommended.

Until full-time pacing is established a tracheostomy tube must remain in place. Even when positive pressure ventilation is no longer required, the tracheostomy stoma must be kept open for occasional suctioning, since these patients cannot cough effectively, and also for a reinstitution of positive pressure breathing should the pacemaker fail or ventilation become inadequate as with severe bronchitis or pneumonia. Following removal of the tube a Teflon button is carefully fitted to the tracheostomy stoma* (Fig. 5).

TABLE 6. *Quadriplegia: Phrenic Nerve Conduction Studies**

Conduction time	Right side msec	Left side msec
Preop	12	12
Postop		
4 mon	9.6	11
16 mon	10	10.6

Data given for R. S., age 52 years, 11 months following C_3-C_4 injury.

Discussion

This review of 37 quadriplegics who have undergone diaphragm pacing has pointed up certain problems in the

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* Obtainable from the Quinton Instrument Co., 3051 44th Ave., W., Seattle, Washington. The diameter of the tracheal stoma and the distance from the skin to the trachea should be measured and furnished the supplier.

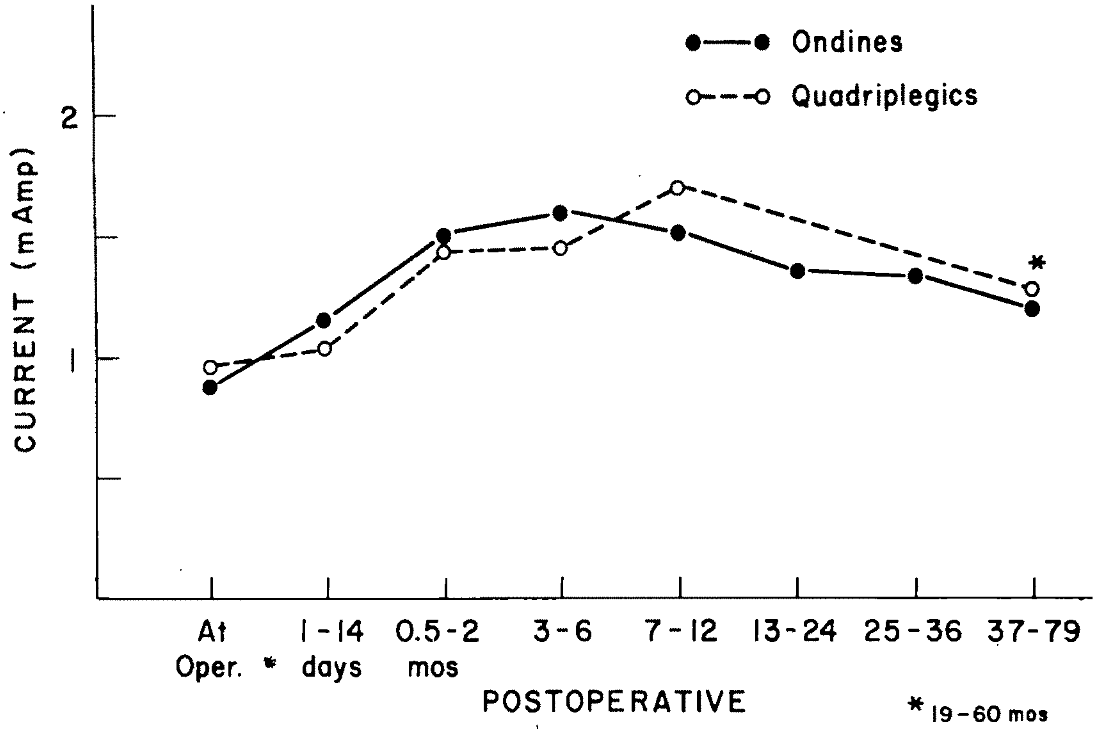

FIG. 6a. Current required to produce minimum contractions (threshold) of the diaphragm in the authors' series of patients with central alveolar hypoventilation (Ondine's Curse) and with quadriplegia. In one quadriplegic patient the threshold on the right rose to 5mA two months postoperatively and then decreased markedly. Threshold values for this one nerve are not included on this graph, but are shown in Fig. 3.

selection of patients, in the techniques of applying the apparatus, especially to the phrenic nerve, and in the management of patients once diaphragm pacing has started.

In the selection of patients it was apparent, and expected, that the level of injury to the cervical cord would influence the viability of the phrenic nerves, reflecting the fact that the phrenic nerves arise from the anterior horn cells in the C3, C4 and C5 segments. Damage to these segments impaired or totally destroyed function of the phrenic nerve in some of the patients and electrical stimulation of the peripheral nerve in such was,

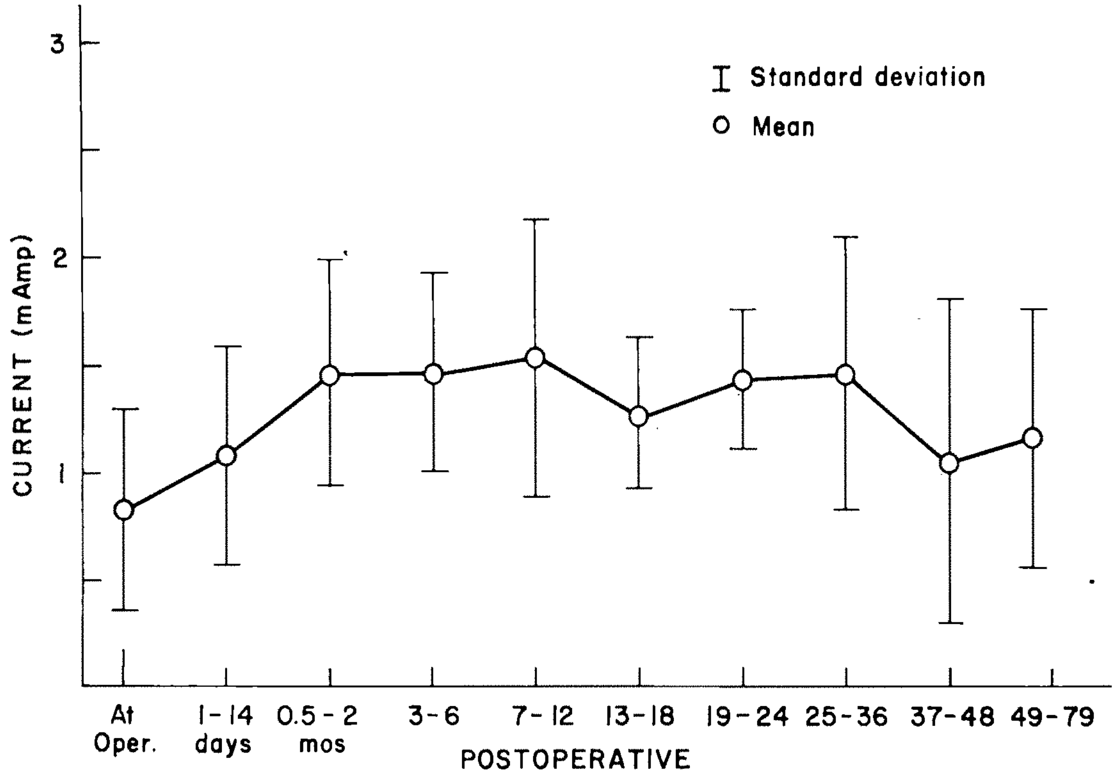

FIG. 6b. Mean values and SD with the series combined.

of course, ineffective. When C3, C4 or C5 segments are damaged and full-time ventilatory support is needed but cannot be achieved by pacing the diaphragm, pacing for even 50% of the time will reduce the risk of respiratory complications and increase the patient's mobility.

The resumption of voluntary respirations following respiratory paralysis secondary to cord injury was seen twice in the series. One patient has continued to do well though paralysis below the C5 level persists. The other patient died in his sleep, presumably from respiratory arrest, 4 months after resumption of voluntary respiration. It is likely that weakness of respiratory muscles persisted and although ventilation was adequate during waking hours apparently it was not while he slept. As the ventilatory response to hypercapnia or hypoxemia may be depressed in patients with chronic ventilatory insufficiency, night-time pacing must be continued until repeated blood or alveolar gas measurements show that ventilation during sleep is adequate.

Operative trauma to the phrenic nerve was a serious problem. This is not surprising when one considers with what ease this nerve can be damaged. Undoubtedly the problem is due in large part to the difficulty of applying the cuff to the nerve and fixing it to the tissue. Nevertheless, the fact that total ventilatory support which is dependent upon an essentially normal response of both phrenic nerves to stimulation has been accomplished in 13 patients for an average of 26 months is indicative that the cuff electrode can be placed atraumatically. Modification of the design of the electrode to make it easier to apply to the nerve is being actively pursued in the research laboratory.

If a nerve is damaged at operation the injury may not be recognized until pacing is attempted 12 to 14 days later. If nerve function is impaired it is probably advisable to explore the cuff and remove it if it appears to be compressing the nerve. When injury to the nerve is not evident the cuff may be left in place. Two quadriplegic patients whose nerves were probably injured at operation and in whom the cuff was not removed showed partial to complete return of function 12 to 16 months later. Conduction time in the phrenic nerves should be determined before operation and periodically thereafter. In one quadriplegic patient with a suspected injury of the left phrenic nerve at operation the conduction time remained prolonged postoperatively whereas the conduction time in the normal right nerve showed the usual postoperative shortening.[19] Sixteen months later there was evidence of return of function in the injured nerve by an increase in diaphragmatic motion and the phrenic nerve conduction time was now about the same as in the opposite nerve (Table 6).

Injury to the nerve due to the electrical stimulus has not been demonstrated in these patients. The average current required to cause minimal contraction of the diaphragm (threshold) increased for the first 6 months of pacing and has since declined. The relatively small number of observations made on our 9 quadriplegic patients was compared with a larger number made on 31 patients with central alveolar hypoventilation paced nightly for 10 to 14 hours. Except for the uniquely high level of current required to pace one side of the diaphragm in one of the quadriplegics (Fig. 3), the current requirements of the quadriplegics and the patients

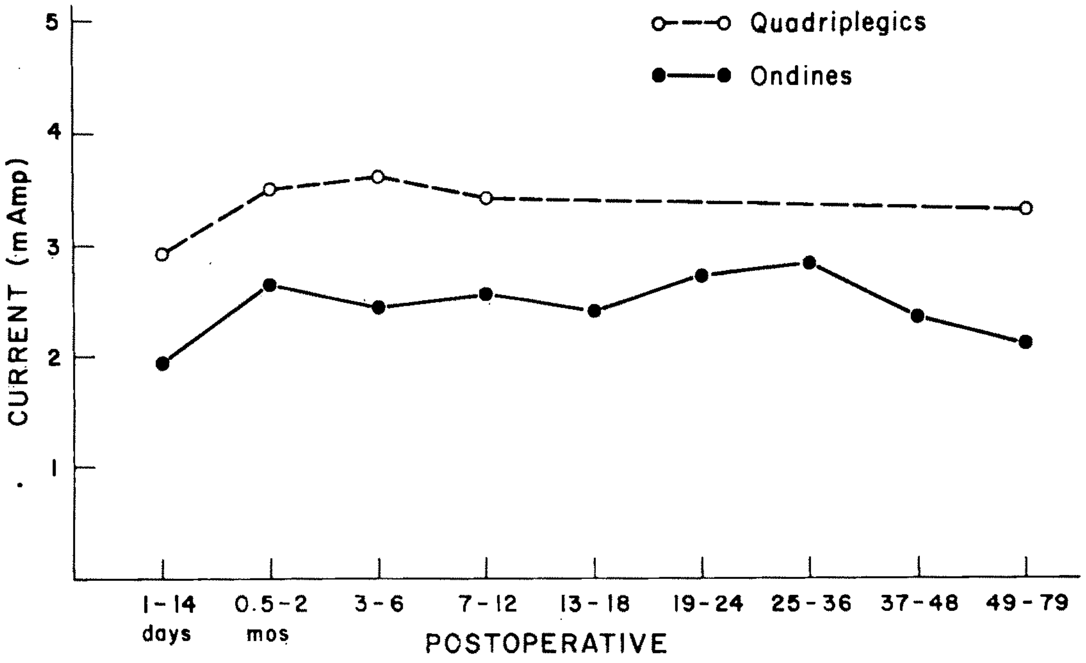

FIG. 7a. Current required to produce maximum contractions of the diaphragm in the authors' series of patients with central alveolar hypoventilation (Ondine's Curse) and with quadriplegia.

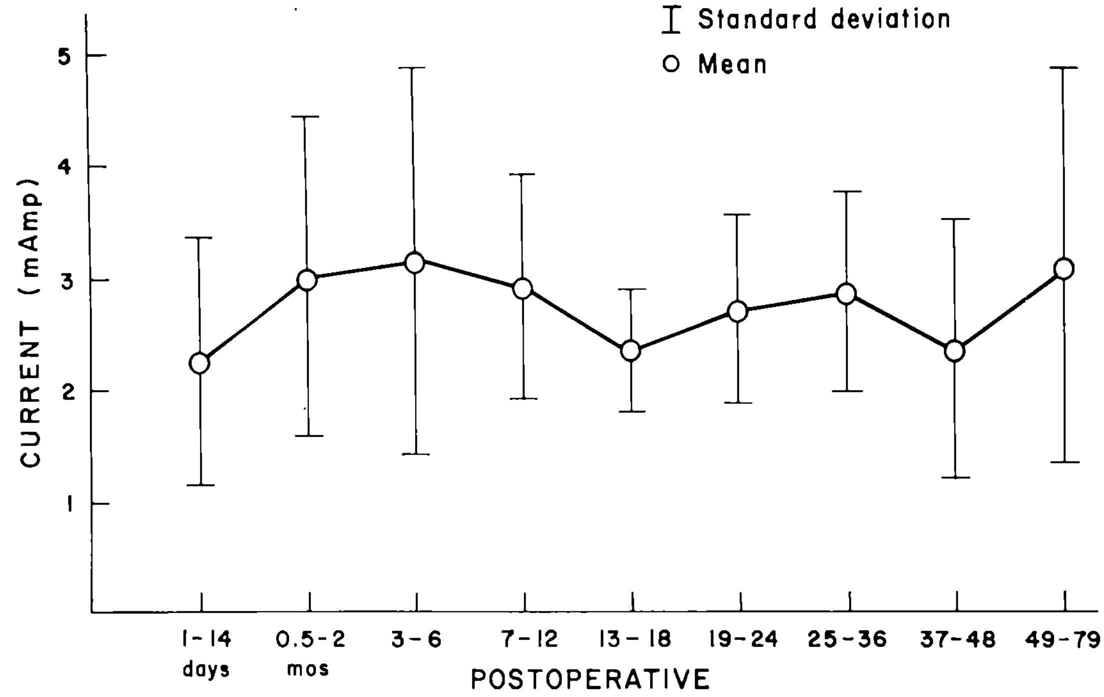

FIG. 7b. Mean values and SD with the series combined.

with Ondine's Curse have been almost identical (Fig. 6). On the other hand, the current required for maximal contraction of the diaphragm was definitely greater in the quadriplegic patients (Fig. 7).

The length of time from the injury to the start of pacing did not appear to influence the length of time required to achieve full-time (12 hour) pacing. In fact, the patient in whom this interval was longest, 11 years, required only 6 weeks of conditioning to achieve complete support of respiration for 12 hours on stimulation of the right nerve. Satisfactory pacing on stimulation of the left nerve was not achieved, either because of injury to the nerve or its cell bodies in the initial accident or traumatization of the nerve at operation. Several other patients whose injury was received 3 or 4 years prior to phrenic nerve stimulation achieved full-time ventilatory support by pacing within a few months.

It is significant that 8 of the 10 deaths in this series occurred in patients in whom it had not been possible to establish satisfactory pacing. It is also significant that 5 of the 8 deaths were due to respiratory tract infections (Table 7). The incidence of respiratory infections in the quadriplegic who is on full-time support by diaphragm pacing and who has a plugged tracheostomy stoma is probably no greater than in the normal population.

Pain on diaphragm pacing is an abnormal finding. It may appear in the neck if the pacing current is high. The sudden onset of pain in the neck during stimulation, as was observed in two patients, was associated with a malfunctioning receiver and was corrected by replacement. Pain in the chest or abdomen was reported by two patients. In both cases operative injury to the phrenic nerve had been suspected.

The principal aim of most of these individuals is to leave the hospital. As one expressed it for all when asked how her pacemaker helped her, she said, "It keeps me out of the hospital and off the MA-1." Nevertheless, the rehabilitation of the quadriplegic who is no longer completely dependent on a positive pressure respirator creates new problems for the patient and his family. The emotional adjustment can be difficult, especially for the younger patients, but where there is an understanding and compassionate family these patients can be encouraged to participate in many activities, including school and even gainful employment. It now becomes the responsibility of the family to take those precautions necessary to protect the patient from infections, particularly those arising in the urinary tract and secondary to decubitus ulceration. The patient and his family should be thoroughly familiar not only with the operation of the positive pressure apparatus, which must always be in readiness in case the pacemaker fails, but also with the operation of the pacemaker. These patients must be provided with a fail-safe alarm system.

TABLE 7. *Causes of Death*

Infection	
Respiratory	5
Septicemia	1
Meningitis	1
Unknown	
Sudden death	3

Conclusions

A new attitude toward the quadriplegic with respiratory paralysis appears to be justified. It is not known for how long the phrenic nerves can withstand electrical stimulation by the present method. Five years is a good beginning. It can be expected that more sophisticated, less traumatic techniques of stimulation of the peripheral nerves will be developed that will provide electrical substitution indefinitely for central nervous system control of respiration.

Acknowledgments

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DISCUSSION

DR. A. ROBERT CORDELL (Winston-Salem): Being able to place an electrically stimulating electrode around the phrenic nerve without producing iscehmia or loss of its function is an accomplishment.

I'd like to pose a couple of questions to Dr. Glenn, and the first is: Can indications for the use of diaphragmatic pacing be extended to include some of the patients who might be comatose on a supposedly temporary basis after trauma, for example, or in patients who have chronic obstructive pulmonary disease, or in certain other trauma victims, even including some patients with chest trauma who might be allowed to be taken off continuous ventilatory control by virtue of this adjunct?

My second question is: Could the concept of so-called "demand use" of diaphragmatic pacing work to advantage in some patients with, for example, the possibility of sensing respiratory rate or blood gases as a method of long-term, continuing control, when necessary by this method?

DR. GILBERT S. CAMPBELL (Little Rock): I first became interested in prolonged ventilatory support when I was in Minnesota during a polio epidemic in 1947. It's impossible to recognize the real worth of this paper unless you realize that patients with chronic hypoventilation are literally imprisoned, either in tank-type respirators in the old days, or attached to volume controlled ventilators in today's time.

DR. LESTER R. BRYANT (New Orleans): I rise primarily to ask Dr. Glenn a couple of questions about the indications for use of the diaphragm pacers. I think many of us are unsure about the selection of patients who might benefit. The publication of this paper may encourage some of our colleagues to request that we see patients who are potential candidates, and I want to ask Dr. Glenn to give us his thoughts in two categories.

To illustrate the questions, my service was asked recently to see a 40-year-old woman at Charity Hospital in New Orleans, who has been the victim of demyelinating disease, and who is dependent on the respirator for her life. The two questions are: Is there any relationship between the patient's socioeconomic background and the likely success of diaphragm pacing? And, are the demyelinating nervous diseases contra-indications for the application of phrenic respiration?

You mentioned one case, I believe, of syringomyelia, but I believe it would be helpful for me and for others to know whether you have formed some idea in your own mind about the indications for phrenic respiration in demyelinating diseases.

DR. W. W. L. GLENN (Closing discussion): Dr. Cordell, so far as temporary pacing is concerned, I do not think that there is any place for the techniques that we have illustrated here today for a temporary problem, because of the possiblity of injury to the nerve. It may be that temporary pacing will have a place if it can be perfected by the transvenous route, such as has been advocated by Escher, Daggett and others. But I think that at present we can only say that positive pressure respiration is probably a safer technique for the treatment of acute, reversible hypoventilation.

With regard to the development of a demand diaphragm pacemaker, this is entirely feasible. As a matter of fact, only a few days ago we studied a patient with Ondine's Curse whose pCO_2 built up very rapidly when he went to sleep. By continuously sampling the air from his nose and passing it through a CO_2 analyzer it was a simple matter to construct a circuit to turn on the diaphragm pacemaker when the CO_2 rose above a certain level.

I might also mention here that it has also been possible to develop a totally implantable diaphragm pacemaker.

Dr. Bryant, as far as the indications for diaphragm pacing go, we have confined this therapy to patients who have either chronic hypoventilation on the basis of central alveolar hypoventilation or on the basis of paralysis of respiration usually secondary to transection of the cervical cord.

As far as the demyelinating diseases are concerned, I don't know the answer to this, exactly. If respiratory insufficiency is due to an upper motor neuron lesion, the phrenic nerves should be viable. Prior to implantation of a pacemaker, viability of the phrenic nerve should be ascertained by Sarnoff's technique of percutaneous stimulation in the neck.

I would like to add a word of caution for those who might want to use this technique. Injury to the phrenic nerve at the time of operation for placement of the nerve cuff has been seen a number of times. I believe that the cuff-type electrode (and its method of application) is the culprit. We have no evidence that electrical stimulation of the nerve as used during pacing causes permanent damage.

If I might have ninety seconds to show you a movie, it will give some of you here who have not seen diaphragm pacing an idea of how it works.

This is a patient with quadriplegia, who has two units in place. There is the one of the left side, and there is the other one on the right. This is to show you the various kinds of diaphragm movement one can obtain with pacing. As you can see, both sides of the diaphragm can be paced together, singly, or alternating from one side to the other.

It is only by coincidence that the receiver is at about the level of the diaphragm. This just happens to be a convenient place to implant it. The phrenic nerve electrodes pass from the receiver up into the neck on either side. Most quadriplegic patients pace 12 hours on one side then 12 hours on the other. A few patients prefer the alternate mode, one side and then the other. Continuous pacing of both sides simultaneously should only be used for short periods, usually when the patients are sitting.

One must always be aware of the fact that fatigue of the nerve will occur with electrical stimulation. To minimize fatigue the rule of thumb is to allow the nerve as much time without stimulation as with.

Functional Tumors of the Organ of Zuckerkandl

FRANK GLENN, M.D.,* GEORGE F. GRAY, M.D.†

From the Cornell University Medical College
and The New York Hospital, New York

Chromaffin-reacting pheochromocytomas of the adrenal medulla are the most frequently encountered functional paraganglionic neoplasms. However, extra-adrenal pheochromocytomas as well as non-chromaffin paragangliomas, including those of the carotid body and glomus jugulare, may produce symptoms from catecholamine secretion. One of the extra-adrenal sites from which these tumors arise is from a collection of para-aortic, paraganglion cells around the origin of the inferior mesenteric artery. This collection of paraganglia was described in fetuses by Zuckerkandl[59] in 1901 and has subsequently been referred to as the organ of Zuckerkandl. The diagnosis and management of these neoplasms differ somewhat from that of adrenal pheochromocytomas, but excellent results are often obtained by excision of these lesions. Four patients with functional tumors of the organ of Zuckerkandl are reviewed together with the other reported cases in the literature.

SINCE 1961 4 instances of functional tumors of the organ of Zuckerkandl have been treated at The New York Hospital-Cornell Medical Center (NYH-CMC). We have found only 46 other instances of organ of Zuckerkandl neoplasms, which can be considered in 3 groups: those discovered at autopsy, those treated surgically by removal of the tumor and those in which operation was embarked upon but the tumor was not removed (Tables 1 to 3).

Group I: Tumors discovered at autopsy. Of 14 tumors, 8 in males and 6 in females, the age range was 15 to 81 years with a median of 53 years. Three tumors (21%) were considered malignant; the remaining 11 (79%) were classified as benign.

Group II: Tumors removed at operation. This is the largest group, 30 in all, 18 males and 12 females. The ages ranged from 15 to 55 years with a median of 32 years. Four (13%) of the tumors were considered to be malignant and 26 (87%) were benign.

Group III: Tumors found at surgery but not removed. There were 6 cases, 2 males, 3 females, 1 not identified. The ages were from 10–60 years with a median of 26 years. Attempted excision was not completed in 2 patients because of intraoperative death. In one case only a biopsy was done and in 3 the tumor was observed and considered inoperable. One of the latter 3 received irradiation and died 11 years later.

The data included in many of the case reports leave much to be desired. The symptoms which led to consideration that these patients had such a lesion are often poorly described and there is paucity of evidence to establish how a diagnosis was made preoperatively. In particular, there is inadequate documentation of whether there was excessive catecholamine secretion by the tumors. Furthermore, followup was not given in 18 of the 30 patients in whom operation was presumably successful. Of the remaining 12, 2 were well 12 years later, 8 were alive 3 years or less after operation and 2 were dead. Thus there is great need for case reporting of those who have a tumor in the organ of Zuckerkandl discovered at autopsy or operation.

Case Reports

Case 1. In 1961, a 17-year-old boy (NYH 89 79 71), previously believed to be well, developed headache and within a few hours collapsed and then had a grand mal seizure. The first physician to see him found a blood pressure of 180/115. At rest after admission to the hospital, the blood pressure was 150/110. Laboratory studies were essentially within normal limits except for total urinary catecholamine excretion which was 2422 μg/24 hr (normal total catecholamines, 200–250 μg/24 hr). A diagnosis of pheochromocytoma was made. The abdomen was explored and a lobulated retroperitoneal tumor was found over the inferior vena cava and abdominal aorta. The vascular supply was by several small arteries, arising directly from the aorta. During manipulation of the tumor, the pulse increased from 110 to 138 and the blood pressure from 140/90 to 150/100. The lesion was removed intact along with 2 adherent lymph nodes. The adrenal glands were uninvolved by tumors. The patient made a satisfactory recovery and is reported to be well 14 years later.

Case 2. A 39-year-old mother of 3 children (NYN 90 12 57) was admitted in 1962 for evaluation of headaches. Her blood pressure was 190/110 and was known to have been elevated for 16 years. Initially, this had been assumed to be related to a toxemia of

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TABLE 1. *Tumors of Organs of Zuckerkandl Revealed at Autopsy*

Author	Patient		Diagnosis
	Age	Sex	
Hausmann[21]	53	M	Benign
Handschin[19]	45	M	Benign
Nordmann[44]	53	M	Benign
Reichardt[49]	53	F	Benign
Cragg[6]	39	F	Benign
Gellerstedt[13]	38	M	Benign
Podloucky[48]	51	M	Benign
Fingerland[9]	71	M	Benign
McCullagh[37]	28	M	Benign
Koster[33]	34	F	Benign
Ortega[46]	81	F	Malignant
Isaacson[28]	15	F	Malignant
Moir[42]	55	F	Benign
Melicow[38]	56	M	Malignant

pregnancy, but urinary catecholamine excretion was high, 332.5 μg/24 hr. Because the adrenal arteries were normal on arteriogram, it was concluded that tumor was extra-adrenal, and at operation, through a long midline incision, both adrenals appeared normal but a hard, nodular tumor lay between the aorta and the inferior vena cava. As the operation was being completed after resection of the tumor, the patient became cyanotic and hypotensive and died despite vigorous resuscitative efforts.

Case 3. In 1966 a 15-year-old boy was found to have an abdominal tumor at the level of the umbilicus. He had been seen as an outpatient over a 4-year period for a variety of complaints, including visual disturbances, dermatitis, minor traumatic injuries, headaches and precardial pain during exercise. A diagnosis was not established; blood pressures were 144/86 and 132/80 at the time the mass was found, but 6 days later were recorded as 200/100. Total urinary catecholamine determination was 1560 μg/24 hr. During induction of anesthesia, the blood pressure increased to 220/160. A retroperitoneal para-aortic mass was found and excised. After clamping the veins, the patient became hypotensive and required intravenous levarterenol for 24 hours. The adrenals appeared normal grossly. The postoperative course was satisfactory with normotension for 3 years, after which followup attempts were unsuccessful.

Case 4. A 21-year-old man (NYH 137 11 02) was known to have "high blood pressure" for 10 years. In 1974 he was explored at another hospital for a lower abdominal retroperitoneal mass which was not removed because of its vascularity and profuse bleeding. The biopsy report was "pheochromocytoma." He was then admitted to The New York Hospital where an aortogram and inferior mesenteric arteriogram showed a vascular tumor extending from just below the right renal artery to the level of the hypogastric artery and extending across the midline, a short distance beyond the left side of the aorta (Fig. 1). The inferior mesenteric artery was displaced by the mass and supplied branches to it. Total urinary catecholamine excretion was 264 μg/24 hr. At exploratory laparotomy numerous vessels supplied the tumor from the aorta and drained into the vena cava. These were divided individually so that the tumor could be raised from its bed. Because of the difficulty in handling the numerous vessels, the operation required several hours of meticulous dissection and numerous transfusions. The postoperative course was uneventful and the patient was free of complaints when last seen 18 months after surgery.

Pathological Findings

The tumors were all lobulated, fleshy masses (Fig. 2). A definitive fibrous capsule was evident in only one tumor. The color of the cut surfaces was light brown or reddish-brown. Prominent blood vessels and hemorrhage were seen in 2 cases and cystic degeneration in one. The recorded weights ranged from 78 to 244 grams and the greatest dimension was 10 cm.

Microscopically, all of the tumors had a population of polygonal cells with fairly uniform, round to oval nuclei and a faintly, slightly granular, indistinct, eosinophilic cytoplasm which tended to be arranged in alveolar nests surrounded by a richly vascular connective tissue stroma

TABLE 2. *Surgical Excision of Tumor*

Author	Patient		Diagnosis	Followup
	Age	Sex		
Strangl[55]	32	M	Benign	—
Bauer[1]	40	M	Benign	—
Fullerton[12]	27	M	Benign	Well, 2 yr postop
Richardson[50]	28	M	Benign	—
Molinatti[43]	24	F	Benign	—
Forssel[10]	38	F	Benign	Recurrence, 12 yr postop
Cook[4]	31	M	Malignant	—
Cook[4]	42	F	Benign	—
Cook[4]	37	M	Benign	—
Heubner[24]	52	M	Benign	—
Holsti[26]	53	M	Malignant	Died, 10 mon postop
Holsti[26]	24	F	Malignant	Improved, 1 mon postop
Mintiens[40]	20	M	Benign	Well, 6 mon postop
Van Zyl[58]	31	F	Benign	—
Joseph[30]	33	M	Malignant	Metastasis, 33 mon postop
Lulu[34]	32	M	Benign	—
Hillestad[25]	—	F	Benign	—
Cornog[5]	27	M	Benign	Well, 1 yr postop
Malter[35]	55	M	Benign	—
Hendry[23]	52	F	Benign	—
Kinkhabwala[32]	54	F	Benign	—
Kinkhabwala[32]	31	F	Benign	—
Czekala[7]	43	F	Benign	—
Hahn[18]	19	M	Benign	—
Deoreo[8]	16	M	Benign	—
Shepard[52]	28	F	Benign	Well, 7 mon postop
NYH-CMC	17	M	Benign	Well, 12 yr postop
NYH-CMC	39	F	Benign	Death at operation
NYH-CMC	15	M	Benign	Well, 3 yr postop
NYH-CMC	21	M	Benign	Well, 1 yr postop

TABLE 3. *Attempted Surgical Excision (Abandoned)*

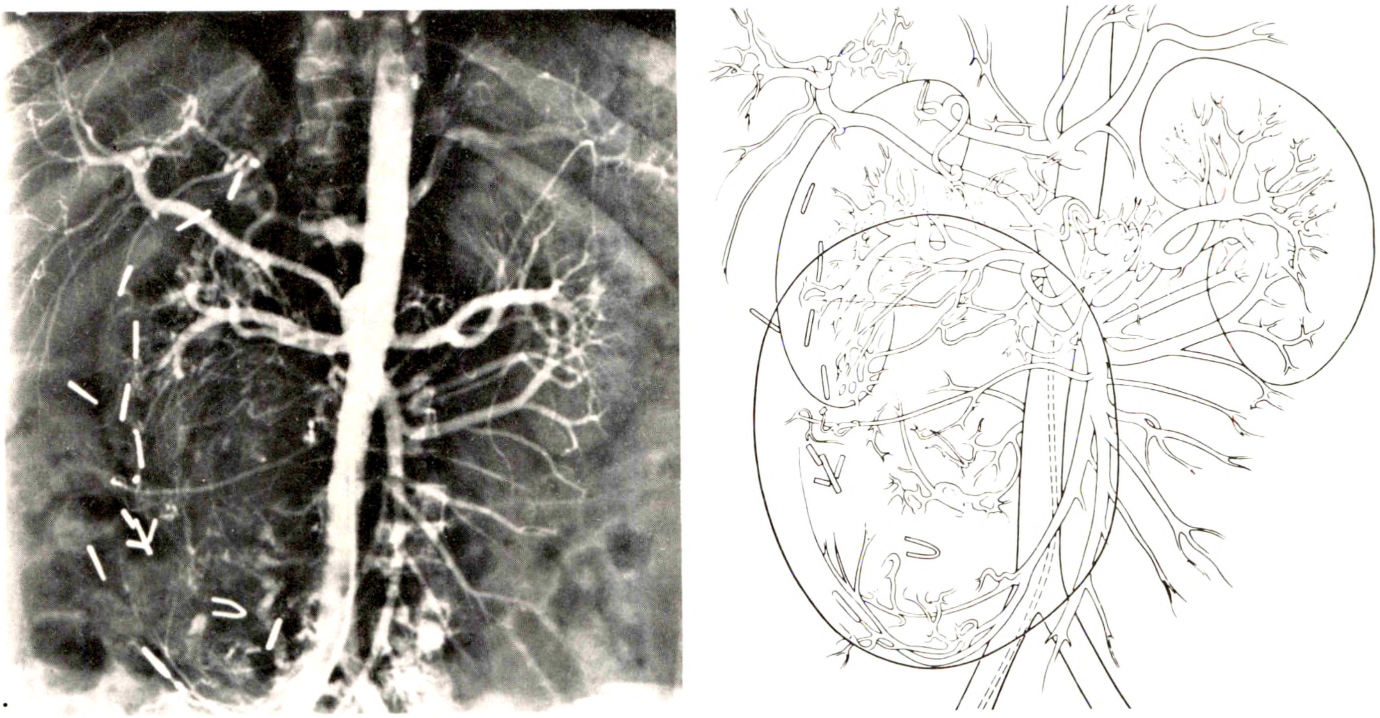
Author	Age	Sex	Operation	Diagnosis	Followup
Merkulow[39]	26	F	Attempted resection	Benign	Dead
Cahill[3]	10	F	Attempted	Benign	Dead
Haug & Baker[20]	60	M	Biopsy	Malignant	Dead, 6 mon postop
Holsti[26]	19	M	Attempted resection	Malignant	Well, 2 yr
Kinkhabwala[32]	—	—	Attempted resection	Malignant	—
Scharf[51]	33	F	Exploration	Malignant	Irradiation Dead, 11 yr postop

(Fig. 3). The appearance of this element is typical of non-chromaffin tumors of the paraganglia. Focally, dense bands of collagen were seen in all of the tumors, accounting for the lobular appearance (Fig. 4). In 3 of the tumors another cellular component was present. This consisted of sheets of cells with more pleomorphic nuclei and a more clearly defined granular, eosinophilic cytoplasm (Fig. 5), which were focally chromaffin-reacting as indicated by fine brown granules in specimen-fixed in Zenker's solution. The nuclei in some instances were bizarre and exhibited mitotic activity focally. These areas were also quite vascular and bands of dense fibrous tissue were also evident in some foci, but the nesting pattern was not present. The appearance of these areas was typical of pheochromocytoma. In a few areas admixtures of the 2 cell types were identified (Fig. 6). Metastasis to a regional lymph node was established histologically in only one instance.

Paragangliomas must be differentiated from carcinoid, hemangiopericytoma, alveolar soft part sarcoma and metastatic carcinoma, particularly thyroid carcinoma. The use of special histologic stains as an adjunct in differential diagnosis is summarized by Glenner and Grimley.[16] In cases of pheochromocytoma of the para-aortic area, a primary tumor in the adrenal medulla must be excluded.

Diagnosis

The symptoms of tumors arising in the organ of Zuckerkandl may be those related either to excessive



FIGS. 1a and b. (left) Aortogram visualizing the inferior mesenteric artery (Case 4). An abdominal aortogram shows a normal celiac axis. The opacified inferior mesenteric artery shows a large and very vascular tumor extending from just below the right renal artery to the level of the hypogastric artery. The right kidney is displaced slightly cephalad and its lower pole is distorted laterally. The tumor estimated to measure 20 cm in length and 10 cm in width rests to the right of the midline extending to the left of the aorta at the level of its greatest diameter.

The inferior mesenteric artery as it courses through the tumor is displaced to the left. It gives off many branches to both the substance and periphery of the mass. (right) Line drawing of aortogram.

catecholamine secretion or to the growth of a retroperitoneal mass.[45] Most of the patients, including all those seen at The New York Hospital, were seen because of excessive catecholamine secretion, and the symptoms in these cases are the same as in adrenal medullary pheochromocytomas. The clinical signs are likely to be headache, fainting and dizziness with hypertension, sometimes paroxysmal, in norepinephrine-secreting neoplasms. In epinephrine-secreting tumors the findings may be irritability, tachycardia, diarrhea, excessive sweating, flushing and possibly also hypertension. Many patients are aware that shift of position or pressure in an area within the abdomen may precipitate episodes. When the tumor arises in the organ of Zuckerkandl, the patient may be subject to paroxysms of hypertension following straining at stool or following ingestion of a large quantity of food or fluid. Palpation of the abdomen may reveal a tumor and pressure on the mass sometimes produces transient elevation of blood pressure.

In the evaluation of symptomatic patients, particularly those with hypertension, the most significant findings relate to elevation of urinary catecholamines and vanillyl mandelic acid (VMA) levels (total catecholamines normal range: 200–250 μg/24 hr; VMA normal range 8–9 μg/24 hr). Elevation of these substances during a period of hypertension as compared with those obtained in a resting period is of diagnostic significance. Blood values in patients with elevated urine determinations may also be of interest, but since those tests are expensive and time consuming, their routine use is not always practical. False positives, that is, patients with consistently elevated catecholamines and no demonstrable tumor, are documented but extremely rare. Provocative tests using histamine or regitine are dangerous and less specific than catecholamine determinations and are no longer a part of our diagnostic work-up.

In 80% of patients with elevated catecholamines, an adrenal tumor is likely to be found by intravenous pyelography. In absence of an adrenal lesion, chest roentgenograms may show a mediastinal tumor. Selective angiograms are most useful in demonstrating tumors arising from the organ of Zuckerkandl, and the evaluation of catecholamine levels of the inferior vena cava and its tributaries may also be of help. Although there has been reluctance in the past to use aortography in evaluation of patients with pheochromocytomas, this procedure is now widely accepted as essential and reasonably safe. Once the diagnosis is established, further confirmation may be obtained by use of blocking agents.

Preoperative Management

Adequate preoperative management is important in preventing the precipitous drop in blood pressure which may follow the release of the longstanding catecholamine vasospasm with sudden increase in vascular space. Preoperative alpha- and beta-adrenergic receptor blockades are invaluable in preoperative preparation. These substances are administered for days or weeks prior to operation, and, properly used, prevent cardiovascular disturbances during induction of anesthesia and the actual excision of the tumor. This is instituted with phenoxybenzamine hydrochloride 1 mg/kg orally and 45 mg of propranolol hydrochloride in 3 doses per day with gradual increases until the blood pressure and tachycardia are controlled. Patients who are well

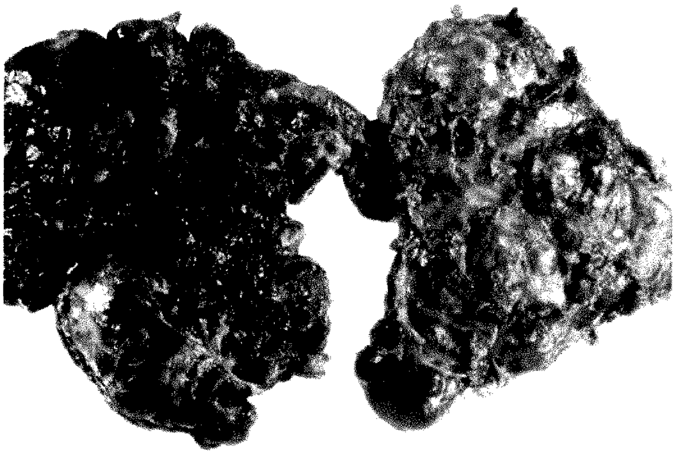


FIG. 2. Functional paraganglioma of organ of Zuckerkandl (Case 4). This was a 244 gm lobulated, reddish-brown, retroperitoneal mass attached by fibrous bands and numerous vessels to the aorta, inferior mesenteric artery and inferior vena cava.

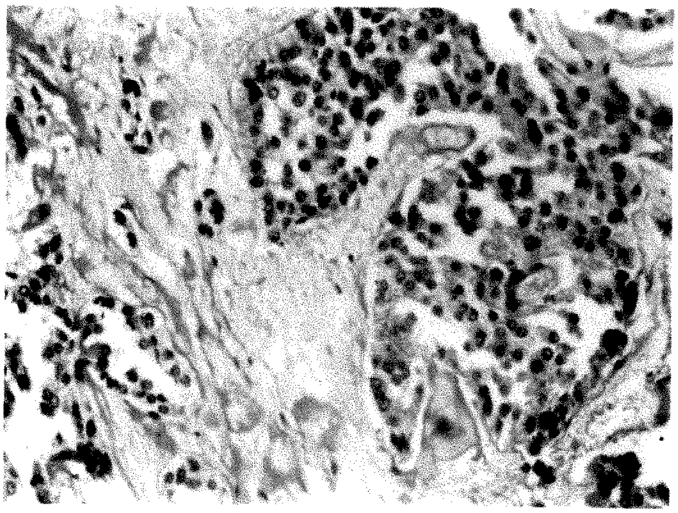


FIG. 3. Para-aortic paraganglioma of organ of Zuckerkandl. Alveolar nests of fairly uniform cells with round or oval vesicular nuclei and finely granular cytoplasm with indistinct borders are separated by thick bands of collagen. Cells of this type were the most prominent element in all 4 cases (H & E, ×62).

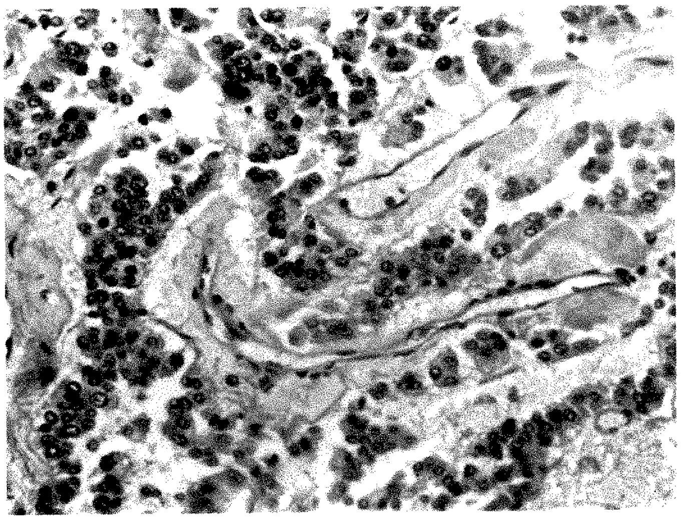


FIG. 4. Abundant blood vessels surrounded by dense collagen bands and separating nests of paraganglioma were seen in all of the tumors (H & E ×62).

prepared usually require less of a beta-blocker if it should be required at operation. The one death among our patients with a para-aortic paraganglioma occurred in 1962 prior to the availability of beta-blocker. Propranolol hydrochloride, which we now use, curtails ventricular arrhythmias that if uncorrected can result in death.

Preoperative medication also includes small doses of barbiturates and of atropine. With adequate preoperative preparation and suitable immediate preoperative medication and propranolol hydrochloride available in the operating room, induction of anesthesia is accomplished with intravenous pentothal. Venous cut-downs are placed so that norepinephrine or other pressor substances may be used at any time during the procedure if a fall of blood pressure occurs with the occlusion of the blood supply to the tumor. Continuous femoral artery pressure measurement by catheter is maintained throughout the procedure.

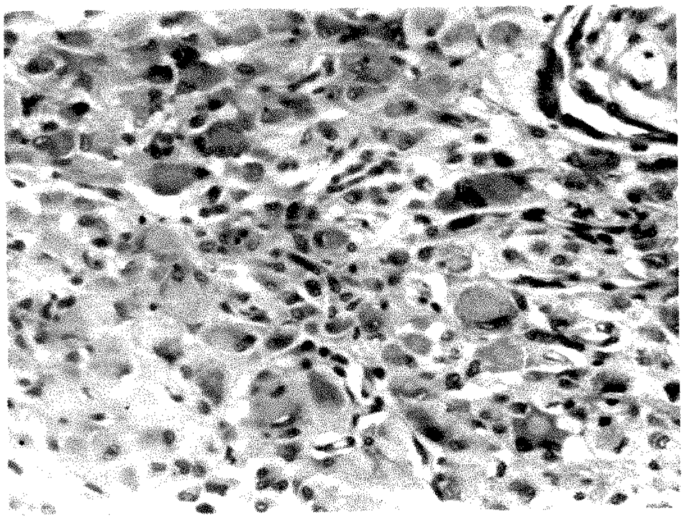


FIG. 5. Pheochromocytoma of organ of Zuckerkandl. Larger cells with distinct borders and granular cytoplasm grow in large sheets. Many of the nuclei are uniform and oval, but some larger, pleomorphic nuclei are seen along with multinucleated forms. Elements of this kind were identified focally in 3 cases (H & E ×62).

Surgical Technique

The surgical approach to tumors arising from the organs of Zuckerkandl is facilitated by generous incisions that provide optimum exposure of the lesion and adjacent structures.

Complete examination preliminary to attacking the tumor includes inspection and palpation of the adrenals and kidneys and demonstration of the course of the ureters from their origin to their junction with the urinary bladder. There may be displacement of these by the tumor if it is large. The second and third portions of the duodenum may also be distorted or displaced.

The relationship of the inferior mesenteric artery and its branches is to be anticipated and identified. The chief blood supply is usually from a number of vessels directly from the aorta. A comparable number of vessels extend directly from the posterior surface of the tumor to the inferior vena cava. These arterial and venous vessels tend to fix the tumor to the aorta and vena cava. Division of these vessels and the individual ligation of each is a tedious endeavor (Fig. 7).

The occlusion of the large vessels and their tributaries beyond the extent of the tumor and followed by division of the communicating vessels and then attempting to secure them as the occluding clamps are gradually released is even more difficult because of retraction of the small arterial branches into the wall of the aorta. These may not be apparent if the blood pressure falls to hypotensive levels. Then as the pressure returns to normal, bleeding tends to occur. During the operation of excising this type of tumor, occluding the return blood supply with its pressor substance contributes to lowering of blood pressures. Loss of blood may further accentuate the hypotension.

Discussion

Frankel[11] in 1886 was the first to postulate that a tumor of the adrenal was the cause of a malignant hypertension that resulted in the death of an 18-year-old girl upon whom he performed an autopsy. Mayo[36] presented the first report in English of a successfully treated case. In 1927 he operated upon a patient who had a large flank tumor, following excision of which there was a moderate, but not dramatic, fall in the blood pressure. It was possible to maintain the patient's vital signs by using intravenous saline, since at that time the pressor substances presently available were not in common use. Two years later, Pincoffs[47] made the preoperative diagnosis of a functioning paraganglioma in a

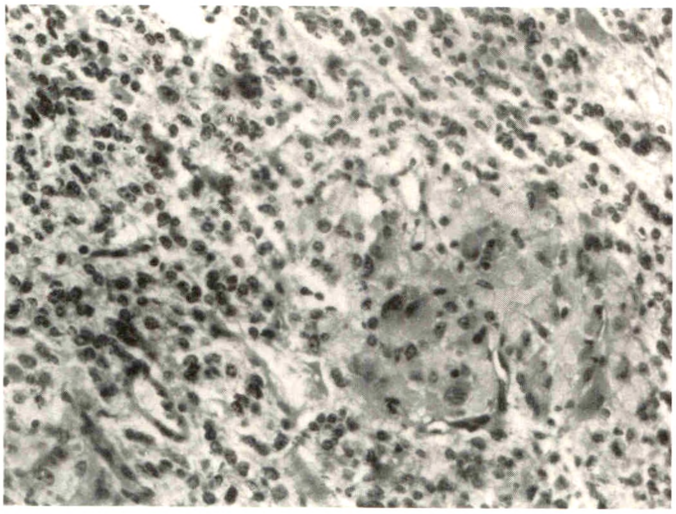


FIG. 6. Mixed cellular population in organ of Zuckerkandl tumor. A nodular cluster of pheochromocytoma type (lower right) is surrounded by paraganglion type cells. (H & E ×62.)

26-year-old woman who had repeated bouts of paroxysmal hypertension. After resection of the 115 gm right adrenal tumor by Shipley,[53] the blood pressure remained at very low levels but the patient recovered uneventfully and had a relatively normal life. Subsequently, further reports in the literature indicated that these tumors were being diagnosed with somewhat increasing frequency. The first adequate review was a collection of 207 cases published in 1951 by Graham.[17] At that time 125 patients had been subjected to surgery with 33 operative deaths. Seventy-two cases were not diagnosed before death, and it appeared that at least 44 of these patients died as a direct result of the hypertension. This would give an overall mortality up to 1951 of approximately 37%.

Between 1951 and 1960 many authors reported their experiences with pheochromocytomas. In 1960 Hume[27] collected over 700 cases from the world literature. He reported that as a result of the more frequent consideration of this diagnosis, the mortality rate was dropping steadily. Since 1960 several other large series of case reports have appeared in the English literature, the largest being the experience with over 100 patients at the Mayo Clinic published in 1966.[56]

Stackpole[54] in 1963 reviewed the experience of the Columbia-Presbyterian Medical Center and the world literature concerning this disease as it affected children. He also found that this disease was a more virulent and rapidly progressive one in children and that constant vigilance was necessary if the mortality rate was to be reduced. Many physicians, however, still fail to suspect pheochromocytoma as a cause for convulsion, elevation in blood pressure, fainting, intermittent blindness in children and therefore, it remains a particularly serious problem in this age group.

In the 1930's it became evident that many pheochromocytomas, probably at least 10%, were extra-adrenal, and that the most frequent site was in the region of the origin of the inferior mesenteric artery. Ortega[46] in 1952 published a report of a malignant paraganglioma arising from the organs of Zuckerkandl and summarized 14 reported tumors which were similarly located. Of 14 previously reported cases all but one were benign. The one malignant case could not be identified.

Retrospective studies then brought attention to Zuckerkandl's description in 1901 of paired bodies of extra-adrenal chromaffin cells near the origin of the inferior mesenteric artery. Bonnamour and Pinatelle[2] in 1902 confirmed Zuckerkandl's observations and described chromaffin bodies in children up to the age of 6 years. In 1912 Zuckerkandl[60] reviewed the literature relating to chromaffin tissues and the postnatal fate of these structures including tumor formation. Ivanoff[29] in 1925 de-

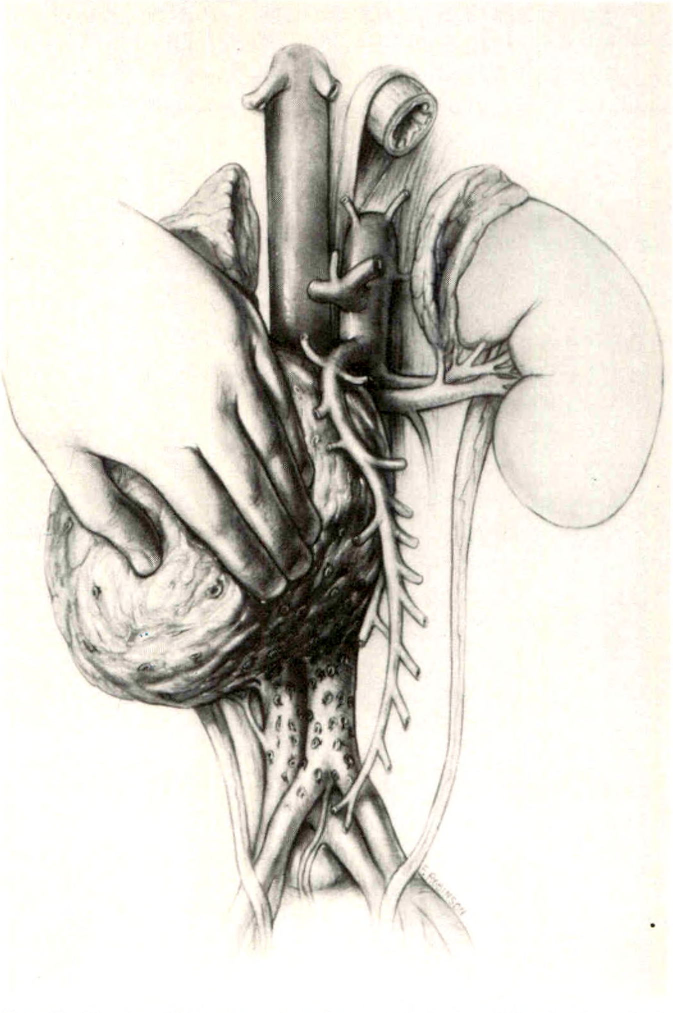


FIG. 7. At operation numerous short vessels were demonstrated to supply the tumor from the aorta. Comparable venous communications drained into the vena cava. These required individual division and ligation to mobilize the tumor, a tedious and time consuming endeavor.

scribed the development and postnatal degeneration of the paraganglia. Wrete[58] in 1927 observed the continuity of the chromaffin bodies of the para-aortic region with the chromaffin tissue of the adrenal glands. In the same year Keene and Hewer[31] observed the common origin of the intra- and extra-adrenal chromaffin cells from the sympathetic anlage.

The recent monograph of Glenner and Grimley[16] summarizes development of the concept of a system of paraganglia including the adrenal medulla and extra-adrenal chromaffin and non-chromaffin tissues. All paraganglia develop from neural crest and migrate with elements of the autonomic nervous system to para-axial locations in association with autonomic ganglia. The paraganglia are more prominent in infancy and, except for the adrenal medulla, are inconspicuous in adults. Branchiomeric paraganglia, including the carotid bodies and glomus jugulare, appear to function primarily as chemoreceptors. Aortico-sympathetic paraganglia, including the adrenal medulla and para-aortic ganglia (the organ of Zuckerkandl) are specialized for secretion of catecholamines, although catecholamine storage granules are demonstrable in all paraganglia. Many instances are reported of tumors arising from the carotid body and glomus jugulare, and paraganglionic tumors have been documented in larynx, mediastinum, lung, orbit, vagus and bladder. Those of the adrenal medulla and organ of Zuckerkandl often have functional activity related to excessive secretion of pressor substances. In addition, tumors of other paraganglia, including the branchiomeric group, occasionally secrete catecholamines in quantities sufficient to produce symptoms. Glenner *et al.*[15] documented functional carotid tumors and Mitsuguahi *et al.*[41] have reviewed functional jugular paraganglioma (glomus jugulare tumor).

The histologic pattern of para-aortic (Zuckerkandl) paragangliomas varies and may be either as the non-chromaffin, paraganglioma (carotid body) type or as chromaffin pheochromocytoma type or as mixtures of these elements. The paraganglioma pattern was present in all 4 of our cases and was the most prominent type in the 3 cases with mixed histologic patterns. Histologic appearance is inconsistently related to catecholamine secretion since both chromaffin and non-chromaffin tumors may be functional. Although non-functional, non-chromaffin tumors are well documented, we have found no well established instances of a non-functional, para-aortic chromaffin tumor. Unfortunately, assessment of histologic type in many of the reported cases is impossible. Histologic appearance is also an unreliable measure of malignancy and benignancy of Zuckerkandl tumors. Pleomorphism, bizarre nuclear forms and mitotic figures are common findings in pheochromocytomas and do not necessarily connote metastatic potential. Likewise, nuclear uniformity and circumscription may be seen in non-chromaffin tumors with nodal metastases. The only reliable criteria for diagnosis of malignancy is demonstration of invasion of adjacent organs or of metastases. Because of the dense adhesions between many of these tumors and surrounding tissues, assessment of invasion is often difficult. Even nodal metastases do not necessarily indicate an aggressive tumor, as indicated by the long term survival of one of our patients (Case 1), with tumor found in a lymph node nearby the primary tumor. Nevertheless, the finding of tumor within a lymph node indicates the malignant potential of some of these tumors.

An estimated 22,950,000 individuals in the United States have hypertension.[22] In a study at the Cleveland Clinic 6% of 5000 patients were demonstrated to have a cause that could be successfully treated surgically.[14] Of these, functioning pheochromocytoma is one of the most favorable for the surgeon to approach, since removal of those tumors that are benign results in a cure. However, 10–15% of catecholamine secreting neoplasms are extra-adrenal, and the largest number of these arise from the organ of Zuckerkandl.

The relative young ages of the patients we have studied and of those reported by others indicates that hypertension in children and young adults merits most meticulous evaluation to permit diagnosis and treatment of a functional paraganglioma before development of irreversible sequelae.

Addendum

Since this paper was submitted, Patient 4, 20 months following his first operation has had an epidural metastatic paraganglioma removed from the L4-5 interspace. The pathological specimen is identical with the primary tumor.

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Discussion

(Note: Some of the discussants' remarks refer to both this paper and to the one following by Dr. H. William Scott, Jr.)

Dr. William H. ReMine (Rochester, Minnesota): When we reviewed our experience before this group two years ago, we had at that time 14 extra-adrenal pheochromocytomas, [slide] and as this has been known to be the 10% tumor, ours came out to be right on the button on 10% of the total group, as you can see.

In reviewing our extra-adrenal pheochromocytomas, this was the distribution as we found them to be at that time. Since this paper was reported, and these figures accumulated, we have had additional cases of this type. One was in the glomus jugulari at the base of the skull. As you know, chromaffin tissue and paraganglia tissue can occur from the base of the skull all the way to a point deep in the pelvis. This particular one at the base of the skull that I removed had been operated upon previously, before he came to us, for a presumed brain tumor because of headaches. The surgeon had removed the top of the "iceberg" where it had extended through the jugular foramen into the base of the brain. By the time he got to us, all of the extracranial nerves on that side had been severed. It was a rather difficult procedure to remove the tumor from the left side of his neck.

Now, this brings up the point that Dr. Glenn and Dr. Scott have pointed out; the value of arteriography, or angiography, in the location of these tumors, especially those that are in the extra-adrenal position. Those that are in the adrenal position, in our experience, have been rather readily located if they are as much as 1½–2 cm in diameter by nephrotomography. But, if they are not located rather easily in this manner, I think angiography is the procedure of choice and it can be a great deal of help.

We had one that I operated on last year that was completely surrounding the celiac axis, about 6 cm in diameter. Angiography is of great value for tumors in this location because you should be prepared to go all the way to bypass procedures, including the use of a graft if you need to, in order to remove the tumor. So you may need the aid and advice of your vascular surgeons if you are going to get involved in this type of tumor surgery.

My last point is this. This is an extra-adrenal pheochromocytoma in the organ of Zuckerkandl. This was a young girl, 18 years of age, and as we were putting her on the table she said, "You don't remember me. I've been married since I met you. But just a year and a half ago you did this same operation on my father." The picture of her father's tumor is quite similar to this patient's.

In view of the great interest in the M.E.N. syndromes that is evolving nowadays, with the multiple endocrine neoplasia problems and the tendency to notice a great variety of hereditary development of these, it would be well worth our while to follow up on other relatives of these patients to determine if there are more of them in the same family that could be diagnosed earlier.

Dr. Richard T. Myers (Winston-Salem): Each of these very excellent presentations has indicated the hazards associated with the management of patients with pheochromocytoma.

A more convincing demonstration of the lethality and potential hazard of pheochromocytoma cannot be made other than teaming it up with pregnancy. In a worldwide survey in 1969 of 89 patients who have had concomitant pheochromocytoma and pregnancy, there were 43 maternal deaths and 39 fetal deaths; a third of these were found at autopsy.

Recently we had a pregnant patient who had a pheochromocytoma involving the organ of Zuckerkandl, and the management of this case might be worthwhile presenting, since it supports some of the very important principles that have been elucidated here today.

(Slide) This was a 36-year-old para 3, gravida 2 woman, who, in the thirtieth week of pregnancy, developed headaches and grand mal seizures. The interesting aspect of her symptomatology was that it occurred when she was lying down, and she felt reasonably comfortable when she was up and about.

She was admitted to the hospital. Her blood pressure ranged as high as 230/120 mm Hg, and fluctuated widely in the elevated ranges during the four to five days it took us to make the differential diagnosis. She had elevated metanephrin and catecholamines, but because of her pregnancy, we could do no angiographic studies. We began giving her dibenzyline and within a few days she became normotensive.

We discharged her from the hospital for a period of 41 days, to allow the fetus to mature. Her blood pressure was normal when she was then readmitted for a Cesarean section. Dibenzyline was discontinued the day before the section and spikes of elevated blood pressure were controlled with phentolamine.

At operation we found that she did have a tumor of the organ of Zuckerkandl, and you can readily see that when she was lying down, the tumor would stimulate secretion in that organ.

The final slide is an artist's depiction of the operative findings, showing the tumor overlying the aorta, and being richly supplied by circulation from the aorta, the vena cava and the ovarian vein.

I would like to congratulate the authors on two very fine papers which emphasize the principles of proper diagnosis, accurate localization, and pharmacological control to allow safe and elective removal of these very hazardous tumors.

Dr. Alton Ochsner, Jr. (New Orleans): These are certainly two very interesting papers, and the remarks I have to make will be directed to Dr. Glenn's paper.

I have had no experience with removing a tumor from the organ of Zuckerkandl, and after seeing the case that he presented, I can see that it would be quite a challenge; so much so that it would seem to me that temporary occlusion of the aorta, the iliac arteries, and the vena cava, proximally and distally, would be in order to control hemorrhage and prevent release of catecholamines into the systemic system. I would appreciate Dr. Glenn's thoughts about this.

Dr. Frank Glenn (Closing discussion): The additional extra-adrenal tumors of the Mayo Clinic are of particular interest to me. They have had the largest experience and with great success in the management of these patients. They have emphasized well the necessity of adhering to the principle, in approaching tumors arising from the endocrine system, adrenal, parathyroid, or what not, to look at places other than their common location and to seek an additional tumor after having found one.

Dr. Myers mentioned a very interesting patient, a pregnant woman with a pheochromocytoma, and I have an idea that if we had pathology reports on some of the past deaths associated with hypertensive crisis during delivery, they might reveal tumors arising from the organ of Zuckerkandl.

The importance of angiography cannot be overemphasized. It seems to me that our radiologists today are more proficient than they have ever been. Some ten to 15 years ago I objected to the attempted visualization of the adrenals, because I had seen one patient with a postvisualization thrombosis of the entire adrenal. It was a difficult situation. In recent years we have employed this method with increasing frequency without an untoward complication and enthusiastically endorse it.

The control of bleeding by clamping the vessels proximal and distal to a tumor arising from the organ of Zuckerkandl is not without danger, in my opinion. With the occlusion of the blood supply there is a fall of the blood pressure; this can be controlled by pressor substances. As you divide the individual vessels to the tumor they retract. With the removal of the clamps proximal and distal to the tumor control of blood loss from the small vessels to the tumor then requires figure of eight suture rather than simple ligature. I prefer to clamp and ligate the vessels individually. This can be a prolonged procedure. Nevertheless Dr. Ochsner, I think your suggestion is a very logical one, and I'd be interested in your experience and that of others with it.

The persistence of hypertension after the removal of a pheochromocytoma, in the elderly person in particular usually is an indication that the removal of that tumor was too long postponed.

One of the reasons for emphasizing the careful evaluation of youngsters with hypertension, seeking a pheochromocytoma, is the excellent end results. Whereas, if you have a fixed hypertension pathological changes are usually nonreversible.

I concur with the discussers that severe hypertension renders preoperative preparation, including blocking agents mandatory. However we must bear in mind that the surgical treatment is not to be postponed indefinitely. We have observed massive myocardial ischemia to occur in patients with pheochromocytomas under optimal circumstances at bed rest in the hospital awaiting operation. Blocking agents have of course greatly reduced this hazard.

Finally it is suggested that the provocative tests used in years past are unnecessary with the availability of catecholamine determinations.

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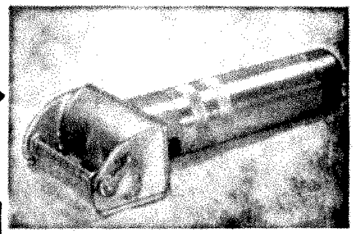

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Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: Tigan is indicated for the control of nausea and vomiting.

CONTRAINDICATIONS: The injectable form of Tigan in children, the suppositories in premature or newborn infants, and use in patients with known hypersensitivity to trimethobenzamide are contraindicated. Since the suppositories contain benzocaine they should not be used in patients known to be sensitive to this or similar local anesthetics.

WARNINGS: Tigan may produce drowsiness. Patients should not operate motor vehicles or other dangerous machinery until their individual responses have been determined. Reye's Syndrome has been associated with the use of Tigan and other drugs, including antiemetics, although their contribution, if any, to the cause and course of the disease hasn't been established. This syndrome is characterized by an abrupt onset shortly following a nonspecific febrile illness, with persistent, severe vomiting, lethargy, irrational behavior, progressive encephalopathy leading to coma, convulsions and death.

Usage in Pregnancy: Trimethobenzamide hydrochloride was studied in reproduction experiments in rats and rabbits and no teratogenicity was suggested. The only effects observed were an increased percentage of embryonic resorptions or stillborn pups in rats administered 20 mg and 100 mg/kg and increased resorptions in rabbits receiving 100 mg/kg. In each study these adverse effects were attributed to one or two dams. The relevance to humans is not known. Since there is no adequate experience in pregnant or lactating women who have received this drug, safety in pregnancy or in nursing mothers has not been established.

PRECAUTIONS: During the course of acute febrile illness, encephalitides, gastroenteritis, dehydration and electrolyte imbalance, especially in children and the elderly or debilitated, CNS reactions such as opisthotonos, convulsions, coma and extrapyramidal symptoms have been reported with and without use of Tigan or other antiemetic agents. In such disorders caution should be exercised in administering Tigan, particularly to patients who have recently received other CNS-acting agents (phenothiazines, barbiturates, belladonna derivatives). It is recommended that severe emesis should not be treated with an antiemetic drug alone; where possible the cause of vomiting should be established. Primary emphasis should be directed toward the restoration of body fluids and electrolyte balance, the relief of fever and relief of the causative disease process. Overhydration should be avoided since it may result in cerebral edema.

The antiemetic effects of Tigan may render diagnosis more difficult in such conditions as appendicitis and obscure signs of toxicity due to overdosage of other drugs.

ADVERSE REACTIONS: There have been reports of hypersensitivity reactions and Parkinson-like symptoms. There have been instances of hypotension reported following parenteral administration to surgical patients. There have been reports of blood dyscrasias, blurring of vision, coma, convulsions, depression of mood, diarrhea, disorientation, dizziness, drowsiness, headache, jaundice, muscle cramps and opisthotonos. If these occur, the administration of the drug should be discontinued. Allergic-type skin reactions have been observed; therefore, the drug should be discontinued at the first sign of sensitization. While these symptoms will usually disappear spontaneously, symptomatic treatment may be indicated in some cases.

NOTE: The injectable form is intended for intramuscular use only; it is not recommended for intravenous use.

HOW SUPPLIED: Suppositories, Pediatric, 100 mg, boxes of 10. Suppositories, 200 mg, boxes of 10 and 50.

Ampuls, 2 ml, boxes of 10. Multiple-Dose Vials, 20 ml. Thera-Ject® (Disposable Syringes), 2 ml, boxes of 10. Capsules 250 mg, bottles of 100 and 500; 100 mg, bottles of 100.

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Side effects are not unknown in patients taking Tigan, but these effects are seldom sufficient to require withdrawal of therapy. (Please see prescribing information.)

The instruction, "Tigan 200 mg I.M., p.r.n. q6h for nausea" on your patients' charts should help keep their recovery smooth and unruffled by disturbances either from emesis or from antiemetic side effects.

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References: 1. Sturdy, J.H., Baird, R.M., and Gerein, A.N.: Ann. Surg. *165*:128, 1967. 2. Tinker, M.A., et al.: Ann. Surg. *180*:831, 1974. 3. Dimmick, J.E., et al.: N. Engl. J. Med. *292*:685, 1975. 4. French, M.L.V., et al.: Surg. Gynecol. Obstet. *137*:465, 1973.

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The Kantrex®
(kanamycin sulfate)
record:

Percent in vitro susceptible to kanamycin.*

	1970	1971	1972	1973	1974
E. coli	90.8	90.5	89.9	90.0	92.0
proteus sp.	89.5	89.5	88.4	90.0	91.0
klebsiella sp.	86.9	86.6	87.9	90.0	93.0
enterobacter sp.	90.5	90.1	90.2	91.4	92.0
serratia sp.	39.2	60.1	72.3	75.6	80.0
herellea sp.	83.2	86.8	87.0	88.4	91.0
mima sp.	78.1	73.9	76.5	74.4	78.0

*Susceptibility data from records based on over 250,000 isolates annually from 180 different hospitals. No in vivo correlation is claimed from the in vitro data.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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(11) 6/18/74

> **Warning:** Irreversible deafness can occur. Tinnitus or vertigo may also occur and indicate vestibular damage and impending deafness. The risk is sharply increased with renal dysfunction. In such cases, decrease size and frequency of doses. Discontinue kanamycin and check hearing if azotemia increases. Watch carefully for ototoxicity in older patients and patients receiving more than 15 Gm. of kanamycin. To avoid neuromuscular paralysis with respiratory depression, postpone intraperitoneal instillation in post-operative patients until recovery from anesthesia and muscle relaxants is complete. Although there have been isolated reports of respiratory depression following intraperitoneal instillation of kanamycin, there is no conclusive proof that this side effect can be produced with recommended doses of the drug. Avoid concurrent use of other ototoxic drugs including ethacrynic acid. Safety in pregnancy is not established.

Indications: Serious infections due to susceptible strains of E. coli, Proteus sp., E. aerogenes, K. pneumoniae, Serratia marcescens and Mima-Herellea. Culture and sensitivity studies should be performed.

Contraindications: A history of hypersensitivity to the drug. Prior auditory damage by kanamycin or other agents may be a contraindication if effective, alternative therapy is available.

Precautions: Obtain audiograms before and during therapy in patients with renal dysfunction when treatment lasts more than 5 days. Stop Kantrex if tinnitus or hearing loss occurs. Hydrate patients to prevent chemical irritation of the renal tubules. Assess renal function periodically, both before and during therapy. If signs of renal irritation occur (casts, cells, proteinuria), increase hydration and reduce the dosage or the frequency of dosage if necessary. In azotemic patients, the frequency (in hours) of doses may be obtained by multiplying the serum creatinine by 9. If azotemia or oliguria occur, discontinue therapy. Mycotic or bacterial superinfection may occur.

Adverse Reactions: Nephrotoxicity—albuminuria, presence of white and red cells, granular casts, azotemia and oliguria have been reported.

Ototoxicity—See Box Warning.

Irritation or pain at the injection site, skin rash, drug fever, headache and paresthesias.

Dosage and Administration: The usual dose is 7.5 mg./Kg./12 hours I.M. or I.V. The average adult dose is 1 Gm. daily. The maximum adult total daily dose should not exceed 1.5 Gm. by all routes of administration and the total amount administered should not exceed 15 Gms.

The intravenous route is used only if intramuscular administration is not feasible. The 0.5 Gm. dose is added to 200 ml. of sterile diluent and administered 60-80 drips/minute.

When used as intraperitoneal instillation, the above dose is diluted in 20 ml. of sterile diluent. If possible, instillation should be postponed until after patient is fully recovered from effects of anesthesia and muscle-relaxing drugs.

As aerosol treatment, 250 mg. of Kantrex is diluted with 3 ml. of physiological saline and nebulize.

Kantrex Injection in concentrations of 0.25 percent (2.5 mg./ml.) has been used satisfactorily as an irrigating solution in abscess cavities, pleural spaces, peritoneal and ventricular cavities.

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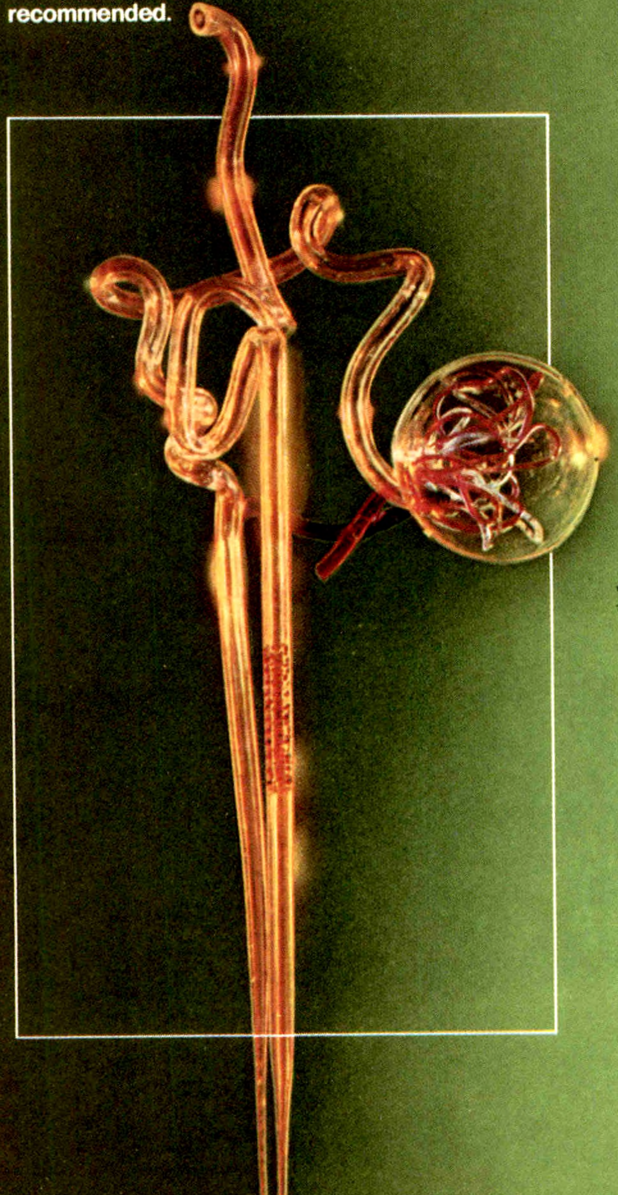
When used as directed, there has been a relatively low incidence of adverse renal or eighth nerve reactions with gentamicin. The risk of such reactions is low in patients with normal renal function who do not receive the drug at higher dosages or for longer periods of time than recommended.



A relatively low incidence of adverse renal reactions

The incidence in 3,370 cases over a period of nearly eight years is shown in the chart below. These patient case studies were derived from clinical research data and the patients were carefully monitored during the treatment period. Most of the adverse renal effects reported were of a transient nature, as demonstrated by elevated blood urea nitrogen, NPN, creatinine, and oliguria.

GARAMYCIN Injectable (gentamicin sulfate) Incidence* of Adverse Renal Reactions

Clinical Investigation Period	1965-1966	1967-1969	1970-Oct.'73
Total Case Studies	285	1,450	1,635
Possibly Related†			
Number	18	49	23
Per Cent	6.3%	3.4%	1.4%
Probably Related			
Number	4	21	25
Per Cent	1.4%	1.4%	1.5%

*Data on file, Schering Laboratories.

†In these cases, no positive evidence exists to indicate whether GARAMYCIN Injectable precipitated the incident or if some other factor was responsible.

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY **Safety for use in pregnancy has not been established.**

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case studies...
# of adverse reactions

A relatively low incidence of adverse eighth nerve reactions

The incidence of adverse eighth nerve reactions in 3,650 cases over a period of nearly ten years is shown in the following chart. These patient case studies were derived from clinical research data and the patients were carefully monitored during the treatment period.

GARAMYCIN Injectable (gentamicin sulfate)
Incidence* of Adverse VIII Nerve Reactions

Clinical Investigation Period	1963-1966	1967-1969	1970-Oct.'73
Total Case Studies	565	1,450	1,635
Vestibular Involvement			
Only	10	18	7
With Impaired Hearing	5	3	1
Impaired Hearing	1	6	7
Total Incidence			
Number	16	27	15
Per Cent	2.8%	1.8%	0.9%

*Data on file, Schering Laboratories.

Two-thirds of these incidents of adverse eighth nerve reactions involved patients with impaired renal function. When occurring in patients with normal renal function, it is often the result of high dosage or longer duration of therapy than recommended. Cases of vestibular involvement reported to date are frequently reversible or compensated for by the patient.

Proper patient management—the key to minimizing the risk of adverse reactions

Identify the "special risk" patient. These patients include those with impaired renal function, elderly debilitated patients, and patients with deteriorating renal function due to either the infection, drug therapy, severe trauma, or major surgical procedures. These important guidelines should then be followed:

1. Follow recommended dosage schedules.
2. Monitor renal function...
   a. in patients with known or suspected renal impairment.
   b. during prolonged therapy.
3. Monitor auditory and vestibular function during prolonged therapy.
4. Adjust dosage intervals in patients with impaired renal function following serum creatinine X 8 formula.
5. Avoid concurrent use of potentially nephrotoxic or ototoxic drugs.
6. Where feasible, monitor gentamicin serum concentrations and avoid prolonged levels above 12 mcg./ml.

In serious gram-negative infections**

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WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (indole-positive and indole-negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS:

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, agranulocytosis, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION
GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:
*Patients with normal renal function**

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lb.), the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

**In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.*

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused over a period of one to two hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., is supplied in 2 ml. (80 mg.) multiple-dose vials and in 1.5 ml. (60 mg.) and 2 ml. (80 mg.) disposable syringes for parenteral administration.

Also available, GARAMYCIN Pediatric Injectable, 10 mg. per ml., supplied in 2 ml. (20 mg.) multiple-dose vials for parenteral administration.

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*Due to susceptible organisms

SLS-596

Pheochromocytoma:

Present Diagnosis and Management

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In the 25-year period 1950–1975 forty-four patients with pheochromocytoma were observed at Vanderbilt University Affiliated Hospitals. Bilateral adrenal tumors occurred in 3 patients (6.8%) and extra-adrenal tumors occurred in 7 others (16%), 33 patients (75%) had single tumors arising in one of the adrenal glands; in one of these 5 years after operation, a malignant tumor developed in the same renal fossa. Five of the 44 patients (11.3%) proved to have malignant tumors and died with metastases. In 11 patients in the earlier years of this study the clinical diagnosis was not made and the tumor was identified by the pathologist at autopsy. There was a single postoperative fatality among the 33 patients in whom the clinical diagnosis was made. Seventy per cent of all survivors with benign tumors have remained normotensive during followup periods of one to 20 years.

PHEOCHROMOCYTOMA is a most hazardous and dramatic cause of hypertension. This potentially lethal neoplasm originates in most cases in the adrenal medulla and less frequently in the cells of the extra-adrenal paraganglion system which are disseminated along the paravertebral axis from the pelvis to the base of the skull. The cell of origin is regarded by Pearse as part of the neuroendocrine group of cells which he calls the APUD series. The cells of this system secrete polypeptide hormones and are, whether by origin or functional similarity, very much alike in character.[4,5] Multiple endocrine neoplasia, type 2, is a genetic disorder involving multifocal tumor formation in this system of polypeptide-secreting cells. Its expressions include pheochromocytoma, medullary carcinoma of thyroid, parathyroid hyperplasia, and multiple oral mucosal neuromas which may occur in combination or singly in several members of a kindred.[8,3] Familial pheochromocytoma also has an association with the neuroectodermal dysplasias which include von Recklinghausen's disease, tuberous sclerosis, Sturge-Weber syndrome and Lindau-von Hippel disease.[2] In these various familial syndromes bilateral adrenal pheochromocytomas tend to occur. However, most frequently the tumor presents as a single lesion of adrenal medullary origin without familial associations.[9]

The incidence of pheochromocytoma has been estimated to range from 0.4 to 2% of all hypertensives. Most tumors occur in adults, but about one-fifth of reported cases have been in children. The reported ages range from 5 months to 82 years. ReMine *et al.* recently reported 138 patients with pheochromocytoma operated on at Mayo Clinic between 1926 and 1970. There were 63 males and 75 females. The tumor was extra-adrenal in 10%, bilateral in 4.4%, multiple in 7% and malignant (proven by metastases) in 18 patients (13.4%).[6]

The clinical manifestations of pheochromocytoma are those which result from the release of catecholamines secreted by the tumor. Epinephrine and norepinephrine are both usually present in adrenal medullary tumors and norepinephrine alone more commonly is secreted by extra-adrenal tumors. Since norepinephrine is a relatively pure alpha adrenergic stimulator and epinephrine has both strong alpha and strong beta adrenergic stimulant effects, clinical manifestations range from hypertension alone to various combinations of tachyarrhythmias and

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Presented at the Annual Meeting of the Southern Surgical Association, December 8–10, 1975, The Homestead, Hot Springs, Virginia.

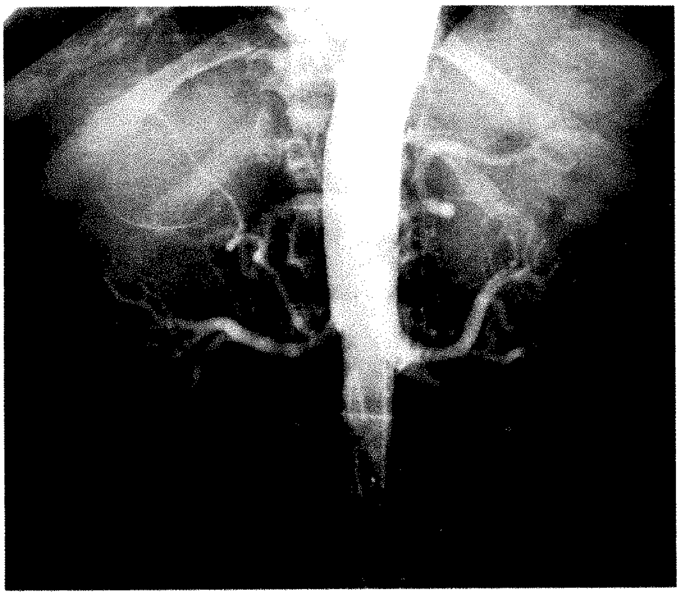

FIG. 1a. Characteristic arteriographic findings in right adrenal pheochromocytoma. Asymmetrically enlarged inferior adrenal artery on right.

hypermetabolic syndromes associated with hypertension. Recognition of the varied clinical manifestations and syndromes is of paramount importance in diagnosis of these tumors. Establishment of accurate diagnosis depends on measurement of abnormal elevations of catecholamines and metabolites in the patient's blood and urine.[9]

This report summarizes the experience in diagnosis and management of patients with pheochromocytoma in the Vanderbilt University Affiliated Hospitals during the last 25 years.

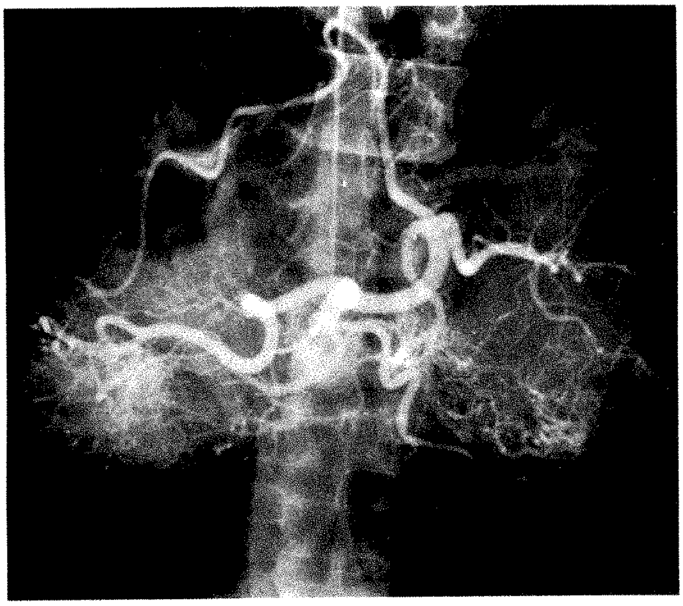

FIG. 1b. Celiac injection with asymmetrically enlarged inferior phrenic artery on right: note tumor vessels below right diaphragm.

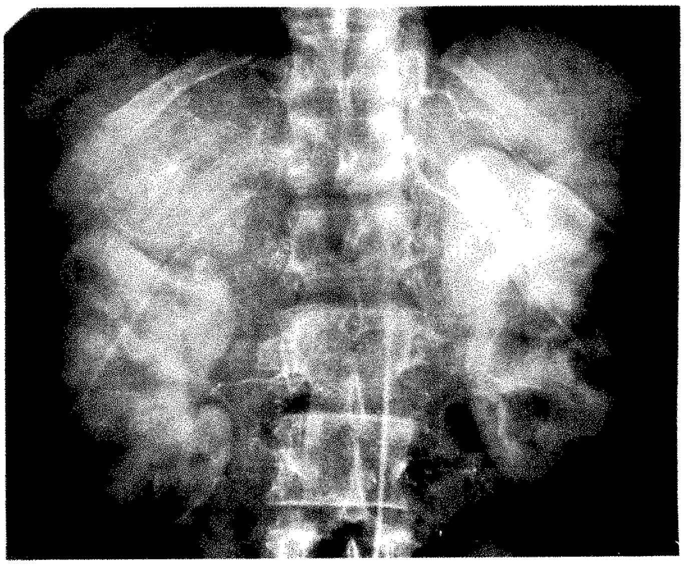

FIG. 1c. Supra-renal mass which flattens upper pole of right kidney. Curvilinear calcification does not indicate true circumference of tumor.

Clinical Experience

In a 25-year period (1950–1975) at Vanderbilt University Affiliated Hospitals (Nashville Veterans Administration Hospital, Nashville Metropolitan General Hospital and Vanderbilt University Hospital) 44 patients with pheochromocytoma were observed. Ages ranged from 9 to 78 years. There were 29 females and 15 males. Familial occurrence of tumors presented as multiple endocrine neoplasia, type 2, in 2 patients and 2 others had the associated findings of von Recklinghausen's cutaneous neurofibromatosis and Lindau-von Hippel disease respectively. The remainder had no familial or neuroectodermal dysplastic associations.

In 11 patients seen in the earlier years of this period of study clinical diagnosis of pheochromocytoma was not made and the tumor was discovered at autopsy by the pathologist.[7] Seven of this group of clinically undiagnosed patients were normotensive. In four patients the pheochromocytoma was an incidental autopsy finding but in the other 7 the tumor contributed to the death of the patient. Two of the former patients were admitted to the hospital for the first time in a pre-terminal state with leukemia and generalized metastases of carcinoma of the cervix, respectively. In the latter group another patient was in a terminal state when first seen with generalized metastases of a nonfunctional, malignant pheochromocytoma of the right adrenal. The deaths in two other normotensive patients occurred in the immediate postoperative period with tachyarrhythmia and shock after salpingectomy for ruptured tubal pregnancy in one and appendectomy in another. One of four hypertensive patients died in a similar manner following hysterectomy. Another hypertensive patient died with a similar arrhythmia and hypotensive crisis three days after he was admitted to the hospital for study which included three repeatedly positive histamine provocative tests. The two remaining hypertensive patients were admitted to the hospital in pre-terminal status with massive cerebral infarctions.

In the 33 patients in whom the clinical diagnosis was established, symptoms of pheochromocytoma had existed for one to 30 years in 17 and from one to 12 months in 15 others. Two patients with medullary thyroid carcinoma from kindreds with multiple endocrine neoplasia (MEN), type 2, were admitted for evaluation and search for pheochromocytomas which were essentially asymptomatic. Except for these two patients, all of this group had hypertension. In 9 patients this was of the sustained variety without evident paroxysmal episodes. In the other 22 patients, paroxysmal attacks were superimposed on sustained hypertension in 9 while 13 had the "classic" pattern of paroxysmal hypertension with normal blood pressure between attacks.

Paroxysmal attacks were characterized by extreme levels of hypertension, severe headache, often described as pounding or throbbing, palpitation, tachycardia, sweating, nausea and weakness. Less often vomiting, hot flashes, visual disturbances and trembling accompanied these episodes. Attacks usually occurred abruptly and persisted for a few minutes to a few hours and often ended with profound weakness.

Physical findings of diagnostic value in these patients were limited. Two patients had sustained paralytic strokes. Two others were nearly blind as a result of hypertensive retinopathy in one and the ocular stigmata of Lindau-von Hippel's disease in the other. Another patient had diffuse cutaneous neurofibromatosis and two others had nodular goiters (MEN, type 2). Three patients who proved to have malignant tumors presented with metastatic lesions of scalp and clavicle. Another patient with a large (425 gm) resectable tumor had a 15 × 10 cm mass in the left upper quadrant.

Laboratory evaluation has emphasized 24-hr collections of urine for free catecholamines, vanillyl mandelic acid (VMA) and metanephrines.[9] Prior to 1955 none of these determinations was available in our laboratories. Urinary free catecholamines were found to be elevated above 100 μg/24 hr in 26 patients. In all but two of these the elevations were repeatedly in excess of 200 μg/24 hr, most commonly in the range of 300 to over 1,000 μg/24 hr. One normotensive patient with MEN, type 2 had low urinary catechols of 118 μg/24 hr and another patient with sustained hypertension who was otherwise asymptomatic had urinary catecholamines of 78 μg/24 hr. Urinary VMA was elevated above 12 mg/24 hr in 14 patients and was below 10 mg/24 hr in three others. Urinary metanephrines have been measured only in the last two years in our laboratories and have been elevated above the normal limit of 1.3 mg/24 hr in

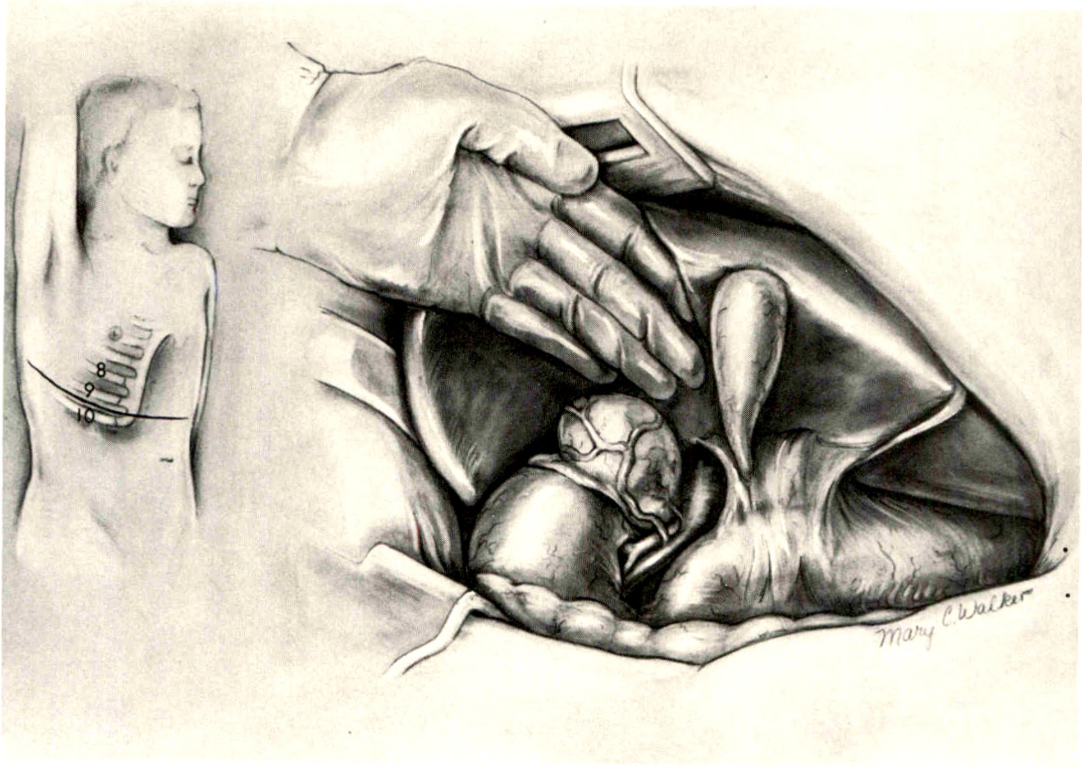

FIG. 2. Exposure of adrenal pheochromocytoma by thoracoabdominal incision, right.

TABLE 1. *Location of Primary Pheochromocytomas*

	Benign	Malignant
Right adrenal	13	2
Left adrenal	19	1*
Bilateral	3	0
Extra-adrenal	5	2
	40	5

* Counted as new malignant tumor 5 years after excision of histologically "benign" pheochromocytoma.

three recent patients. Positive diabetic glucose tolerance tests were found before operation in 9 patients.

Radiographic studies which were helpful in localizing the site of pheochromocytoma before operation included nephro-tomography, intravenous urography, retroperitoneal pneumography, flush aortography and selective arteriography of renal arteries and other aortic branches. Retrograde venous angiography and adrenal vein catheterization for measurement of catecholamines have been rarely used. During the past decade we have come to rely preferentially on contrast arteriography in most patients with suspected pheochromocytoma.[9,1] While rapid injection of hypertonic iodinated contrast medium is a powerful pharmacologic stimulus for catecholamine release from a pheochromoctyoma, if the procedure is carried out with appropriate precautions, including the use of alpha adrenergic blocking agents, monitoring of vital signs and electrocardiogram with full preparation for carrying out whatever resuscitation may be required, excellent results can be safely obtained. Preoperative localization of pheochromocytoma was accurately accomplished in 17 of the 33 patients in whom clinical diagnosis was made (Fig. 1).

Preoperative preparation of these patients in the last decade has usually included the use of alpha adrenergic blocking agents. Phenoxybenzamine and/or Phentolamine have been used for 4 to 10 days in patients with blood pressure of 200/130 or greater or with frequent, severe hypertensive attacks. Beta adrenergic blockade with Propanolol has been added for coexisting arrhythmias, persistent premature ventricular contractions and tachycardia (pulse rate greater than 140/min).[9]

TABLE 2. *Pheochromocytoma: Early Survival*

	Patients	Deaths
Clinical diagnosis made (Surgical removal)	33*	1†
Clinical diagnosis not made (Autopsy)	11	11
Total	44	12

* Two patients had only biopsy of metastatic tumor.
† Renal failure after removal of tumor and left kidney.

Anesthetic management in recent years has begun with adrenergic blockade. Thiopental and nitrous oxide are used for induction with deep halothane anesthesia for maintenance in most patients. A Lidocaine drip is used to control arrhythmias with Phentolamine supplementation if needed. Aggressive blood and fluid replacement are used during operation in anticipation of hypotension after removal of the tumor. Usually 50 to 75 grams albumin and 2 to 3 liters of Ringers' lactate are given. We have tried to avoid the use of norepinephrine because of the hazard of cutaneous sloughs with extravasation at sites of infusion.[9]

Operative procedure has been based on our preference for wide exposure and non-manipulative dissection in removal of pheochromocytomas. An anterior transperitoneal approach which permits examination of both adrenal glands and a search of the para-spinal axis is desirable. With large (>6 cm diameter) tumors, extension of the incision across the costal margin into the eighth or ninth intercostal space greatly improves exposure. We have used a thoracoabdominal incision in the majority of patients with adrenal pheochromocytoma in this series (Fig. 2). There have been no deaths during operation. We believe the safety and excellence of the exposure justify the slight increase in morbidity which accompanies its use.

The location of primary pheochromocytomas in the 44 patients of this series is summarized in Table 1. One patient whose well localized, non-invasive tumor of left adrenal was excised with all of the gland in 1958 was asymptomatic for 5 uneventful years and then an invasive, non-functioning highly malignant pheochromocytoma developed in the left suprarenal fossa. The latter is listed in the "malignant" column and the former listed as "benign." Whether this was a recurrence or a new malignant tumor cannot be determined. Despite radical removal of this malignant tumor, the patient died with metastases in 9 months.

The 11 patients whose tumors were discovered at autopsy and in whom the diagnosis of pheochromocytoma was not made during life are listed in Table 2. Details of their circumstances have been previously reported[7] and are summarized earlier in this article.

Among the 33 patients in whom the clinical diagnosis was made, 31 had removal of primary pheochromocytomas with a single postoperative fatality: a 48-year-old man in 1967 under Penthrane anesthesia had removal of a large (8 × 7 × 3.5 cm) localized tumor which had surrounded the left renal vein and required simultaneous left nephrectomy. He was hypotensive for a brief period at the end of the operation. Subsequently, he went into oliguric renal failure and died in uremia 4 weeks later. All others survived operative removal of the pheochromocytoma (Table 2). In two patients with benign tumors hemorrhagic infarction with spontaneous rupture of the tumor necessitated emergent operations. In two patients with metastatic malignant tumors only biopsy of metastases was done to establish pathologic diagnosis prior to chemotherapy. The primary tumor in these patients was never removed although its site was radiologically localized.

Pathologic classification of pheochromocytomas as benign or malignant (Table 1) is based on the presence or absence of proven metastases. We follow this practice because histologic pattern does not accurately predict biologic behavior. All cases demonstrated the histologic patterns found in pheochromocytoma, including solid alveoli, sheets and anastomosing cords of cells in an endocrine pattern closely related to a rich capillary network.[9]

Non-fatal postoperative complications included atelectasis and pneumonitis in 5 patients; one of these in addition had a persistent pleural effusion and another required reinsertion of a thoracotomy tube because of pneumothorax. In the early years of the study 6 patients required postoperative infusions of norepinephrine for one to 3 days and 2 of these sustained a cutaneous slough at the site of infusion. There were isolated instances of wound infection, urinary tract infection and thromboembolism. One patient sustained a transient hemiparesis. Another who had renal failure prior to excision of the pheochromocytoma developed bleeding from stress ulcers after operation requiring reoperation for control.

The results for patients who survived operative removal of pheochromocytoma have varied with age, familial relationships and the benign or malignant characteristics of the tumor. Both patients with familial pheochromocytoma and those in the childhood age group have an increased tendency to have bilateral tumors as well as synchronous and metachronous multiple extra-adrenal tumors.[6]

Followup has been completed to date (December, 1975) in all but two patients in this series (Fig. 3). In these exceptions a single benign adrenal pheochromocytoma was removed in 1957 and 1963 and each patient remained normotensive and asymptomatic for a period of 11 years and 18 months, respectively, before our loss of contact with them. Each of the 4 patients with malignant pheochromocytoma who were clinically managed received x-ray therapy and various chemotherapeutic agents and died with disseminated metastases 9 months, 2, 3 and 11 years after the diagnosis was made. In two of these patients an histologically benign pheochromocytoma had initially been removed 11 and almost 6 years, respectively, prior to death from metastatic disease.

In the 25 remaining patients with benign pheochromocytoma, up-to-date followup extends from one to 20 years. In this group are the two adults with MEN, type 2, and the only child in the series, a 9-year-old boy with no identifiable familial associations. Each had bilateral adrenal pheochromocytomas removed with satisfactory courses on maintenance steroids in the last one to 4 years. One of the two patients with MEN, type 2, is known to have widely distributed metastases of medullary

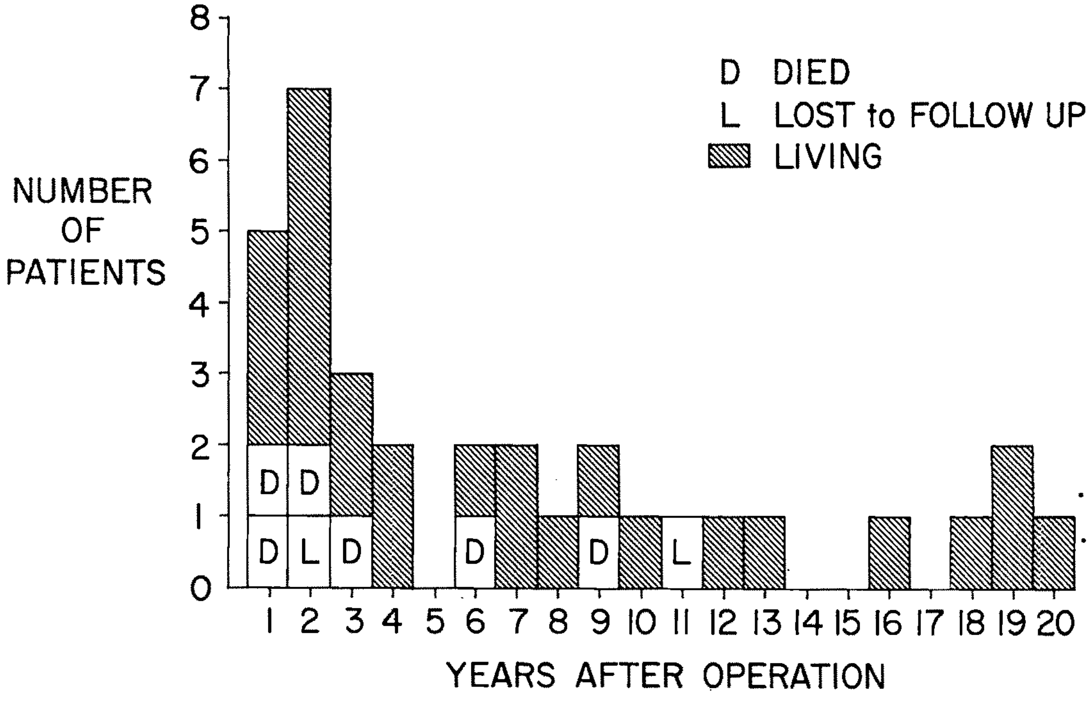

FIG. 3. Followup data in 33 patients with pheochromocytoma in whom clinical diagnosis was made and treatment instituted.

thyroid carcinoma. Each of these 3 patients is normotensive.

Among the 22 other patients who had a single benign pheochromocytoma removed was one woman who had a renal hilar tumor and coexisting renal artery stenosis which was repaired when the tumor was excised. Both she and 12 others in this group who have been followed from 18 months to 20 years have remained normotensive and asymptomatic with no evidence of recurrence of pheochromocytoma. However, in the 9 other patients hypertension has persisted or developed in the period of followup after excision of the tumor. One of these patients had malignant hypertension with diffusely severe renal arteriolosclerosis and nitrogen retention at the time her small para-aortic pheochromocytoma was excised. She sustained no improvement from removal of the tumor and died in uremia 3 months later. Catecholamines were normal after operation in this patient and have been within the normal range in each of the other 8 patients who have developed hypertension during the followup period. In each instance the hypertension has been controlled satisfactorily with antihypertensive drugs. Three of these patients are on Digitalis preparations and one also has an enlarged heart which has been attributed to catecholamine myocardiopathy.

Diabetic glucose tolerance tests which existed before operation in 9 patients have reverted to normal in 7 after removal of the pheochromocytoma.

Comment

We have reviewed the clinical experience with pheochromocytoma at Vanderbilt University Affiliated Hospitals over the last 25 years. Between 1950–1975, 44 patients were observed in whom this diagnosis was histologically confirmed. Bilateral adrenal tumors occurred in 3 patients (6.8%), extra-adrenal tumors occurred in 7 others (16%), 33 patients (75%) had single tumors arising in one of the adrenal glands; in one of these a malignant tumor developed 5 years later in the ipsilateral renal fossa. Five of the 44 patients (11.3%) proved to have malignant pheochromocytomas and died with metastases. In 11 patients in the early years of this study the clinical diagnosis was not made and the tumor was identified by the pathologist at autopsy. There was a single postoperative fatality among the 33 patients in whom the clinical diagnosis was established. Four of these clinically recognized patients died during followup 9 months to 11 years with metastatic disease. Seventy per cent of all survivors with benign tumors have remained normotensive; hypertension has persisted or developed in 30% including one patient with pre-existing malignant hypertension who died in renal failure 3 months after excision of a small pheochromocytoma. All others have normal catecholamines and have been controlled with anti-hypertensive medication.

Pheochromocytoma can simulate any hypertensive syndrome. Although it is an uncommon cause of high blood pressure, all hypertensives should be screened for the tumor. Followup for life is mandatory in all patients with surgically treated pheochromocytoma.

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DISCUSSION

(Note: Some of the discussants' remarks refer to both this paper and to the preceding one by Dr. Frank Glenn.)

DR. ROBERT M. MILES (Memphis): We are indeed indebted to Drs. Glenn and Scott for calling attention to these unusual tumors and newer methods of diagnosis and treatment. The hospital incidence in our area is about 1.3 per 100,000 admissions—certainly a rare tumor.

With angiography and the laboratory determinations referred to, it's a far cry from the situation twenty-five years ago, when we had to depend upon a high index of suspicion and sometimes misleading pharmacological tests. But even the new methods of diagnosis and localization are not perfect, and despite preoperative identification of what is thought to be a pheo, at surgery, which is preferably done through the transabdominal approach, a careful search should be made for additional tumors. We have been surprised on more than one occasion to find extra-adrenal tumors.

(Slide) In this patient we found one on the right side; and this is it, bisected. In addition, we found another in the left adrenal, and an extra-adrenal tumor just above it. That is, three in all. This patient also had a medullary carcinoma of the thyroid, qualifying him for diagnosis of Sipple's syndrome.

(Slide) In another patient, this is the pheo in the organ of Zuckerkandl, between the aorta and vena cava.

Although the alpha and beta blocking agents have simplified management, and have made surgery safer, they are not foolproof. It should be remembered that with propanolol one can titrate the heart rate to zero, if enough is given. One should not take refuge in these agents to the point of delaying surgery unnecessarily. All should be considered urgent. We have seen one patient die the night before surgery was scheduled, and another necessitated emergency surgery at 2:00 a.m. because of rapidly progressing hemiplegia.

As far as location of these tumors is concerned, Dr. Scott mentioned that they may be found anywhere from the base of the brain to the bladder.

(Slide) Actually, they may be found lower than that—in the scrotum. This area should be carefully examined in these patients. If what's thought to be three testicles are found, one should be suspicious of one of them being a pheo.

Dr. John Van Heerden (Rochester, Minnesota): As Dr. Scott stated, two years ago, before this very society, Dr. ReMine and I presented our experience with 130 patients with pheochromocytoma. We are certainly pleased that Dr. Scott and his colleagues have so accurately corroborated our results.

I rise for two reasons: Firstly, to ask Dr. Scott whether any of these patients formed part of the multiple endocrine neoplasia type II syndrome; and perhaps he would like to elaborate on the two patients that he mentioned. And secondly, we would like to emphasize the association of pheochromocytoma in this M.E.N. Type II syndrome.

In 1972, Dr. Jackson, *et al.* postulated that C-cell hyperplasia of the thyroid was a precursor, or a premalignant phase, to medullary carcinoma of the thyroid gland in this familial syndrome. Dr. Aiden Carney, one of our surgical pathologists, has similarly postulated that adrenal medullary hyperplasia might indeed be a precursor to pheochromocytoma in the familial syndrome.

This has been substantiated recently by our opportunity to review the adrenal glands in 19 patients with the M.E.N. Type II syndrome. In these 19 patients, we have found synchronous bilateral pheochromocytomas in nine patients, almost 50% of this group, asynchronous pheochromocytoma in one patient, unilateral pheochromocytoma with contralateral medullary hyperplasia in four patients, bilateral adrenal medullary hyperplasia in two patients, no abnormality in two patients, and unilateral pheo in one more.

The clinical importance of both this association of pheochromocytoma in the Sipple syndrome and the premalignant phase could be summarized as follows. Firstly, as Dr. Scott has pointed out, I believe, undiagnosed pheochromocytoma is responsible for significant mortality in this syndrome. The literature reports up to about 22% of causes of death due to hypertensive crises.

Secondly, we all know that advanced adrenal medullary pathology might be present without clinical manifestations.

Thirdly, as we have stressed before, the biochemical tests, and in particular the provocative tests, for pheochromocytoma might be negative in this familial syndrome.

Fourthly, medullary carcinoma can be now readily identified and diagnosed by serum calcitonin assay.

Fifthly, if adrenal medullary hyperplasia is diagnosed, a bilateral total adrenalectomy should be performed. The first such patient that underwent total adrenalectomy at our institution was operated on by our colleague, Dr. Hugh B. Lynn.

Sixthly, (slide) although we all recognize the patient with the typical familial neuroma phenotype we should remember that the non-neuroma phenotype is also encountered quite commonly in the M.E.N. II syndrome.

Dr. Paul T. DeCamp (New Orleans): There is one item in Dr. Scott's presentation that struck my fancy, and that is he was not distressed by the significant number of patients in whom a diagnosis had been made and adequate surgery had been performed, and nevertheless had persistent hypertension. This did not lead him to a guilt syndrome, that he had misdiagnosed and mistreated these patients.

The application of this to another type of surgical hypertension is, perhaps, in order. Years ago, when we first ran into renovascular hypertension, nobody really knew how to make a definition and to some extent that still exists. This has led to a guilt syndrome, because to this day, in spite of adequate diagnostic techniques demonstrating anatomical changes that are appropriate, and then either pharmacologic or hemodynamic findings which are consistent with the disease, and then appropriate and effective treatment, we still find a residual group of hypertensives.

I would simply urge that we should not feel guilty under these circumstances. Some patients who have had hypertension, for some reason, even though that reason has been removed, may still have hypertension. I feel we can go to bed at night with a clear conscience under those circumstances.

Dr. H. William Scott, Jr. (Closing discussion): I'm concerned, Dr. Glenn, about the terminology, the use of the term "organ of Zuckerkandl" as a specific item today, as it was used when Zuckerkandl described it in 1901. The question I would like to have you answer is whether it is appropriate to restrict the term "organ of Zuckerkandl" to the paraganglia immediately adjacent to the inferior mesenteric artery, as he described, or, indeed, to all the extra-adrenal paraganglia from the base of the skull to the testicle, or the scrotum.

The pathologists at the Armed Forces Institute of Pathology have come forward with a monograph in which they describe a new concept of the paraganglion system; and they, of course, include the adrenal medulla as the largest collection of paraganglionic tissue in the body. It is today, I believe, most appropriate to think of these specialized cells in relation to their hormonal output, the polypeptide hormones that they secrete, and perhaps leave to the past the old terms of the chromaffin and nonchromaffin responses, and not to dwell too much on differences based on histologic staining characteristics.

I congratulate Dr. Van Heerden and Dr. ReMine on their excellent results. We had two patients only who had the multiple endocrine neoplasia Type II syndrome with bilateral pheochromocytomas. Each of these patients had medullary carcinomas of the thyroid—unfortunately, with liver metastases—and each patient has been studied extensively with great interest in their familial relationships.

The comments by Dr. Myers are very well taken. The problem of pheochromocytoma in pregnancy has been catastrophic, and I congratulate him on his handling of this difficult problem.

Dr. Miles made some very sound points about localization and management of the tumors.

And finally, Dr. DeCamp, I am beset by guilt complexes of all types, specifically those related to pheochromocytoma. Thirty per cent of our patients did indeed have persistent hypertension. None of them had elevated catecholamines. Each has been followed and has been managed satisfactorily, with one exception, on antihypertensive medication. To our knowledge, there are no correctable renovascular hypertensive problems in the group.

One patient who did have a pre-existing arteriolonephrosclerosis, with nitrogen retention, had no response to removal of an extra-adrenal pheochromocytoma, and died in uremia about four or five months after removal of this tumor, which accomplished very little for her advanced status.

Predicted Survival in Peptic Ulcer Patients Based on Computer Analysis of Preoperative Variables

GEORGE L. IRVIN, III, M.D., ROBERT ZEPPA, M.D.

A prospective study designed to emphasize and quantitate the operative risk of patients preparing to undergo surgery for the treatment of complicated peptic ulcer disease is presented. Data were gathered from 347 consecutive patients operated on with benign gastric and/or duodenal ulcers in a Veterans Hospital over an 8-year period. Resident surgeons performed all operations and for the most part decided on the operative procedure used, with advice from attending faculty. Preoperative factors influencing the operative mortality in 34 patients were compared with those in surviving patients and subjected to a multivariant discriminant function analysis by computer. Ten variables were identified as being significantly different ($P < 0.05-P < 0.01$) between the survivor and non-survivor groups. Using the discriminant weights of these variables, a computer program was written to calculate the 30-day operative mortality of any preoperative patient based on this past experience. The accuracy of the program is excellent in good risk patients; i.e., a predicted greater than 90% chance of survival was correct 98.9% of the time with 3 deaths in 279 patients. Patients at the low end of the scale (less than 10%) were predicted with 85% accuracy. In the last 8 months, 29 patients have undergone surgery after prospective computer assessment of their operative risk. All have survived with a predicted chance of greater than 50%. Four patients died with survival chances predicted at 4, 2, 1, and 1%. The computer may be used as an educational vehicle for sharpening our preoperative assessment of a patient with ulcer disease, particularly regarding operative risk.

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THE PURPOSE of this study is to emphasize with the aid of computer analysis, the important factors influencing operative risk in patients with complicated peptic ulcer disease. The paper is divided into two parts: 1) a retrospective study of 347 consecutive patients operated on for this disease in the Miami Veterans Administration Hospital from January 1967 through December 1974; and 2) the application of multivariant discriminant function analysis of this retrospective data to a prospective group of similar patients for preoperative asssessment of their operative risks.

Retrospective Material

There are 264 patients with duodenal and 83 patients with gastric ulcers in the series. The type ulcer alone did not significantly influence operative mortality rates within 30 days of surgery in that there were 23 non-survivors with duodenal ulcer disease and 11 with gastric ulcers. Patients with cancer, gastritis or multiple stress ulcers were not included. The mean age was 54 years and 63% of this patient population was over 50 years of age when they received their surgical procedure. The age distribution is shown in Table 1. The 30-day operative mortality of 10% was related to age as shown in Table 2 with a 90% mortality occurring in the 10 patients 80 years of age or over.

The indications for surgery in this series of patients showed that hemorrhage and perforation contributed prominently in the non-survivor group as shown in Table 3. Several patients had more than one indication.

Mortality was also definitely related to operative urgency in that of the 126 patients undergoing emergency surgery, the operative mortality was 25%. There were 221 patients done electively with only two deaths resulting in an operative mortality of 1% which compares favorably with other recently reported series.[1-5] The 168 surgical cases with benign duodenal ulcers done electively all survived, and of the 53 gastric ulcers done electively, there were two operative deaths. On the other hand, if these cases were done under emergency

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TABLE 1. *Age Distribution*

Age	Number	Per Cent
20–29	10	2.9
30–39	31	8.9
40–49	87	25.1
50–59	115	33.1
60–69	71	20.5
70–79	23	6.6
80 and over	10	2.9
Totals	347	100.0

TABLE 3. *Surgical Indications*

Indication	Total	Survivors	Non-survivors
Hemorrhage	157	135	22 (14%)
Perforation	77	64	13 (17%)
Obstruction	57	56	1 (2%)
Intractability	95	95	0 (0%)

conditions the operative mortality was 24 and 30% respectively. The surgical procedure employed did not influence the operative risk factor; of the 126 patients undergoing an elective vagotomy and drainage procedure, there were no operative deaths; and there were only 2 deaths in 89 patients who underwent elective resections. Similarly, in those patients in which these two types of procedures were done under emergency conditions, the operative mortality was much higher but not significantly different at 30% and 24% respectively for vagotomy and drainage versus gastric resection. Forty patients underwent an emergency operation in which a simple closure of a perforated ulcer was performed and this resulted in 8 deaths or an operative mortality of 20%.

There were four major preoperative complications that statistically influenced the outcome in these surgically treated peptic ulcer patients. Pulmonary problems were most frequent with 24 patients having this complication listed as a serious factor. Cardiovascular, renal, and liver diseases were also factors as shown in Table 4. In the 252 patients who had no serious preoperative complications, there was only one postoperative death (Table 5). On the other hand, of the 62 patients with one serious preoperative complication, 24% did not survive, and as the number of complications increased, so did the operative mortality. Moreover, operative urgency was also related to preoperative complications. Of the 252 patients with no complications only 26% were done as emergencies, while 56% of patients with one serious preoperative complication, and 76% having two or more complications were done as emergencies presumedly from a reluctance to subject seriously ill patients to surgery for peptic ulcer disease except under dire circumstances. Postoperative complications, such as sepsis, peritonitis, fistula, recurrent hemorrhage, wound dehiscence, local infection, delayed emptying, blood reaction and recurrence were listed as contributing factors but in no instance was mortality related to one of these complications alone.

With the use of the Univac 1109 computer, a multivariant discriminant function analysis was performed on the data from this retrospective series of patients and the significance of each variable in predicting survival was calculated. Table 6 shows the rank of each contributing variable. Renal disease was weighted highest in that only 3% of the 313 survivors but 41% of the 34 non-survivors had this pre-existing complication. Although hemorrhage was the most frequent indication for surgery, it made the least contribution to the predicted outcome in as much as it was present in 43% of those patients surviving. However, all 10 of the variables listed in Table 6 were statistically significant ($P < 0.01 - P < 0.05$) between the surviving and non-surviving groups. With the data analyzed in this fashion, a program was written for a prospective analysis.

This program is available on many computer terminals but its data base is drawn from the patient population in a particular hospital over the past 8 years. It can be updated at anytime as information on more patients becomes available. By means of a typewriter terminal the computer asks the surgeon several questions concerning the preoperative workup, such as, the patients age; diagnosis; whether the procedure is being done as an emergency or on an elective basis; what the indication for surgery is: obstruction, perforation, hemorrhage, or intractability; and whether any one of four serious preoperative complications are present, including pulmonary, cardiovascular, liver or renal disease. All of these questions can be answered by a number or a simple letter for yes-no on the keyboard. The computer then

TABLE 2. *Age Related Mortality*

Age	Patients	Deaths	Per Cent
20–39	41	0	0
40–49	87	4	5
50–59	115	8	7
60–69	71	7	10
70–79	23	6	26
80 and over	10	9	90
Totals	347	34	10

TABLE 4. *Mortality Related to Only One Preoperative Complication*

	Total	Survivors	Non-survivors
Pulmonary	24	18	6 (25%)
Cardiovascular	18	15	3 (17%)
Renal	13	9	4 (31%)
Liver	7	5	2 (29%)
Total	62	47	15 (24%)

TABLE 5. *Mortality Related to Preoperative Complications*

Complications	Total	Survivors	Non-survivors
0	252	251	1 (0%)
1	62	47	15 (24%)
2	23	12	11 (48%)
3	9	3	6 (67%)
4	1	0	1 (100%)
Total	347	313	34 (10%)

TABLE 7. *Prospective Series*

Preop Predicted Survival	Number Patients	Actual Survival
99–82%	22	22
75–46%	3	3
4%	1	0
2%	1	0
1%	2	0

mathematically predicts the probability of the patient surviving 30 days following surgery based on the 347 previous cases. As an example, one can choose a 75-year-old man with duodenal ulcer undergoing elective surgery for hemorrhage and intractability. One serious preoperative complication is listed in his case as pulmonary disease. Once these data are entered, the computer prediction is printed as an 81% probability of surviving 30 days following operation. As another example, let us assume the same patient presents himself under different circumstances and is operated on with a severe hemorrhage as an emergency. His chances of survival would be predicted by the computer to drop to 35%. To emphasize further the effect of pre-existing diseases, a 65-year-old man with a duodenal ulcer was operated on as an emergency for hemorrhage. With no serious preoperative complications, his predicted survival would be 96%. However, if he also has severe liver disease, the predicted survival would be 88%; cardiovascular, 84%; pulmonary, 45%, and severe renal disease would give him a predicted survival of 2%. To illustrate the influence of two preoperative complications, the same patient with liver and cardiovascular complications preoperatively would be predicted to have a 55% chance of surviving his operation. Pulmonary and liver complications together increase the risk of surgery, and survival would be predicted at 12%. Pulmonary and cardiovascular complications would drive survival to 8% and renal disease along with any other serious complication would be predicted at only 1%.

The accuracy of this program was tested on all of the retrospective patients and was found to be very precise in its prediction of good risk patients. If a patient's operative survival was predicted at greater than 90%, the prediction was correct 98.9% of the time with only three deaths occurring in 279 patients. The computer was not accurate in the middle group of patients with a predicted chance of survival between 10 and 59%. Only 26 patients fell in this group which did not permit differentiation between survivors and non-survivors. On the other hand, the computer was quite accurate in patients in the very poor risk category. The prediction was 85% correct in identifying such patients with less than a 10% chance of surivivng the operation.

TABLE 6. *Contribution of Each Variable in Predicting Survival*

Variable	313 Survivors	34 Non-survivors
Renal	3%	41%
Pulmonary	10%	62%
Age (years)	52 ± 11	67 ± 14
Emergency	30%	94%
Obstruction	18%	3%
Cardiovascular	8%	44%
Liver	5%	27%
Perforation	20%	38%
Intractability	30%	0%
Hemorrhage	43%	65%

Prospective Study

Beginning in January, 1975, a prospective study was initiated based on the computer analysis and the written program to predict survival in all patients undergoing surgery for complicated peptic ulcer disease. Preoperatively, each patient was analyzed by this quantitative program. In the 8 month period there have been 29 patients operated on for the complications of peptic ulcer disease in this hospital. As shown in Table 7, there were 22 patients in whom the preoperatively predicted survival figures ranged from 99 to 82%. All of these patients survived surgery and were discharged. In the 75–46% predicted survival group, there were only three patients and they all survived. However, there were 4 patients who died within 30 days following their surgery. The computer identified each of them quite accurately with the preoperative predicted survival values of 4, 2, 1, and 1% respectively. A brief case summary of each patient is presented to emphasize the seriousness of his illness.

Case Reports

Case 1. W. C., a 58-year-old Caucasian man, was a heavy alcohol consumer and smoker and had poor nutrition, severe cardiovascular and liver disease and moderate pulmonary complications. He had a perforated duodenal ulcer with infected ascites and was in shock. He was seen at 3:30 am, resusitated and underwent emergency surgery at 9:00 am. His predicted survival was 4%. Operation: Closure of perforated D.U.; course: Sepsis, fistula, renal failure, fluid balance difficulties, ascites. He died 15 days postop.

Case 2. O. L., a 77-year-old Caucasian man, had a poor nutritional status, gastric ulcer by endoscopy, moderate pulmonary and severe cardiovascular disease, hemorrhage. He was operated on at 2:00 am after receiving 6 units of blood. His predicted survival was 2%. Operation: Vagotomy, antrectomy, Bilroth II for gastic and duodenal ulcers; course: Massive intra-abdominal hemorrhage from ulcer bed. He died 12 days postop.

Case 3. P. P., a 64-year-old Caucasian man with poor nutritional status, was a light alcohol consumer, heavy smoker, diabetic and had moderate pulmonary and renal complications, carcinoma of prostate, severe cardiovascular problems and a perforated ulcer. Emergency surgery was done. His predicted survival was 1%. Operation: closure of perforated D. U.; course: Cardiac death, 7 days postop.

Case 4. H. D., a 55-year-old Caucasian man, had a duodenal ulcer for 2 years. He was a heavy alcohol consumer, heavy smoker, in a poor nutritional state, and had moderate pulmonary; severe liver, severe renal complications and pancreatic ascites. Hemorrhage required 17 units of blood; failure of the arterial catheter to control hemorrhage resulted in emergency operation. His predicted survival rate was 1%. Operation: Vagotomy, pyloroplasty, oversewing D. U.; Course: Hypotension, cardiac arrest, death in O. R.

Discussion

This paper is not designed to discuss the relative values of the different surgical approaches used for the control of peptic ulcer disease patients. Indeed, elective vagotomy and drainage procedures and resections were done safely with an operative mortality of 1% which compares favorably with recently reported series advocating several procedures in a large number of patients.[1–5] On examining our data, it is also obvious that urgently ill patients undergoing either of these two procedures did not differ in their operative mortality, although patients with a greater risk of surgery, for the most part, had the less time-consuming operation. The fact remains that in this patient population, a great proportion of very severely ill patients underwent a surgical procedure for complications for peptic ulcer disease, and the survival of these patients was dependent more on their coexisting diseases, age and type of ulcer complication than on other factors.

The computer through its capability of statistically rating each one of these factors against each other and computing the probability of a patient surviving a surgical procedure gives us a new educational tool which has certain advantages. For the first time, we can accurately quantitate the risk of a necessary operation based on our previous operative experience. When a surgical trainee evaluates an older patient in the medical intensive care unit who has been on a respirator for long standing pulmonary disease, in renal failure and concomitantly develops hemorrhage from a long standing duodenal ulcer, the trainee can now alter his usual response of "a high risk patient but we will operate to stop his bleeding and maybe save his life" by accurately placing the risk of this patient surviving at only 1%. His judgment would be secure if he elected instead to attempt to stop his hemorrhage with a vasopressor from an indwelling arterial catheter or by other noninvasive methods. Chances of the patient surviving with medical therapy are probably as good as, or better without the added trauma of surgery since he is dying from his coexisting disease.

We can also use this computer analysis to educate our medical colleagues. It should be obvious that delay often exaggerates the risk in patients with peptic ulcer disease. Pointing out the risk factors shown in this analysis to even the most reluctant referring physician should encourage him to reconsider operating earlier and electively on his patients with intractable ulcer disease. A safe, definitive operation offering good control of the ulcer disease before the marked increase in risk that occurs in older patients with coexisting disease is warranted. On the other hand, the group of patients with chronic peptic ulcer disease, with or without associated medical complications, who have not and never will come to surgery for their ulcer disease far exceeds the number operated on either electively or as an emergency. The computer provides a tool which could result in patient selection for elective surgery on rational grounds, and through a prospective, randomized study the accuracy of this rationale can be determined.

The concept of using this type of computer analysis for predicting outcome can certainly be applied to many other surgical problems. In the case of a complicated peptic ulcer patient, such an evaluation is not meant to be the sole deciding factor of whether or not to operate. That decision is still based on subjective clinical judgment. However, it stands to reason that an objective, quantative assessment of a patient's chances of survival, based on the analysis of complications accompanying a disease entity, can only improve our clinical judgment.

Acknowledgment

The authors gratefully acknowledge the technical assistance of Mr. Jack Banbury.

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DISCUSSION

DR. HIRAM C. POLK, JR. (Louisville): For most of this century, surgeons have been infatuated with skills that were expressed as clinical judgment. It's been an indefinable factor. It's been a factor that we could appreciate by its smell, its taste, but we could seldom describe it. We could seldom tell a resident how to acquire it, and, indeed, as one surgeon, who trained Dr. Warren and certain others of us, said: "Most never know it!"

Well, as a matter of fact, excellent clinical judgment is manifest by exactly what Drs. Irvin and Zeppa have presented to us this morning. This is a superb contribution, which goes far in two important areas: 1) to make objective those things that are associated with good or bad short-term results from a common operation; and 2) that this same mechanism can serve as an example we can show students and residents of the ingredients of excellent clinical judgment.

I have nothing to add, except to remind you that this paper is a major contribution in an area that has long been ignored. He has clearly defined the people who are very likely to get well. He has clearly defined those people who are likely to die.

Now, of course, the predominant criticism is to say that the patient who is likely to die is going to die without operation in any case. As a matter of fact, as a first-generation refinement, this is the first step that one must take in order to begin to discriminate that patient who has some characteristic that even the most astute, senior clinician fails to pick up, that's likely to put him in the poor prognostic group. One can then avoid more often unexpected death after an operation under more favorable circumstances.

I assure you that this paper is worth reading in detail, because all of the hypotheses are carefully worked out, and are worthy of being incorporated in all our practice.

DR. GEORGE L. IRVIN, III (Closing discussion): I thought surely there would be more comments about our high operative mortality. It is true, and at the present time we are using this type of related data mainly as an educational tool for our residents and medical colleagues. I hope in the future to apply this type of data gathering and predictability to other disease states.

The Effects on Gastrin and Gastric Secretion of Five Current Operations for Duodenal Ulcer

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We have measured serum gastrin and gastric acid secretion in 66 duodenal ulcer patients before and after vagotomy and pyloroplasty (V + P—15 patients), selective proximal vagotomy without drainage (SPV − D—11 patients) and with drainage (SPV + D—19 patients), and vagotomy, antrectomy, and either gastroduodenostomy (V + BI—15 patients) or gastrojejunostomy (V + BII—6 patients). Basal and peak postprandial gastrin levels were increased in postoperative V + P, SPV − D, and SPV + D patients. Basal and peak postprandial levels of gastrin were unchanged after V + BII, indicative of duodenal release of gastrin. Gastrin response to food was abolished in V + BII patients. Acid output was reliably reduced after all five operations; reduction was greatest in patients after antrectomy and least in patients after SPV. No beneficial results were found with drainage in SPV patients. Acid secretion increased with time in SPV patients, especially those with drainage.

PEPTIC ULCERS are caused by digestion of mucosa by acid peptic juice. Pepsin is inactive above pH 5, so the goal of all ulcer therapy is to achieve an intraluminal pH sufficiently high to prevent peptic digestion. Over the last half century, several operations have evolved for treatment of complications of the duodenal ulcer diathesis; procedures that have been clinically successful have been reliable in reducing acidity. The two major stimuli of acid secretion are the vagus nerve and gastrin. Reduction of acid can be achieved by interfering with either of these stimuli or by reducing the number of parietal cells.

We have been engaged for the last several years in randomized trials designed to compare the results achieved with various operations for duodenal ulcer. In the course of these trials, we have accumulated physiologic data on the effects of various standard operations (truncal vagotomy plus drainage and truncal vagotomy plus antrectomy with either gastroduodenostomy or gastrojejunostomy) and operations that are under trial (selective proximal vagotomy with and without drainage). We will report in this study the effects of these operative procedures on serum gastrin concentration and on gastric acid secretion.

Materials and Methods

We have studied prospectively 66 patients with duodenal ulcer disease who were admitted to The University of Texas Medical Branch Hospitals. The mean age of the patients was 47 years, with a range of 20 to 65 years. The ratio of men to women was 5 to 1 (56 men and 11 women). The diagnosis of duodenal ulcer disease was established for all patients by fiberoptic endoscopy and by radiography.

All patients underwent elective operation for complications of duodenal ulcer disease. No patients were included who had an emergency operation. The chief indication for operation was intractable pain. Most patients had had symptoms for more than 2 years and the range of duration of symptoms was from 4 months to 21 years. Three patients were operated upon electively because of recurrent episodes of anemia that were a consequence of chronic bleeding from a duodenal ulcer, and two were operated upon because of partial gastric outlet obstruction.

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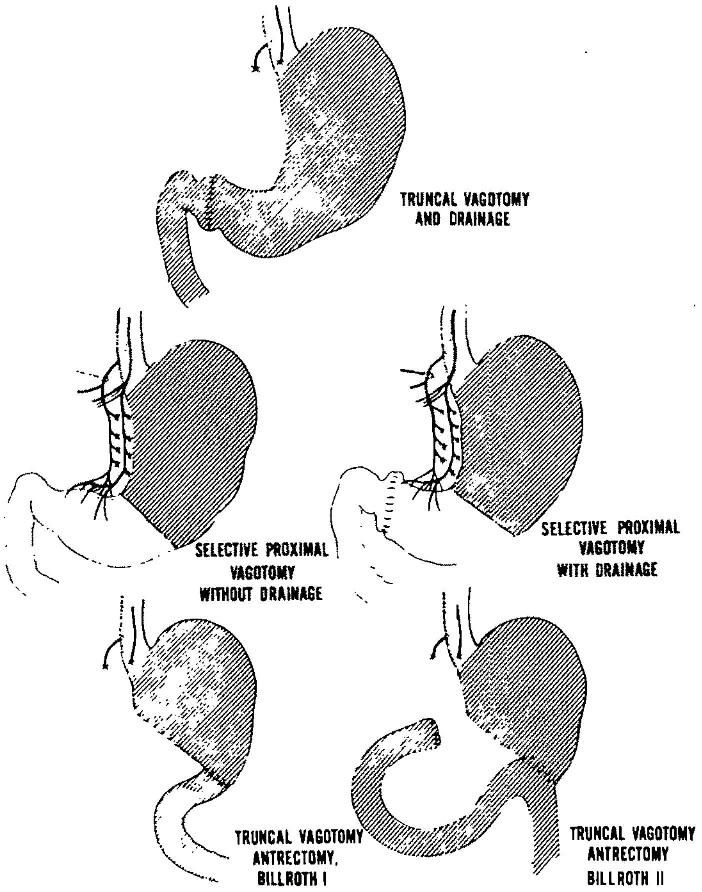
TRUNCAL VAGOTOMY AND DRAINAGE
SELECTIVE PROXIMAL VAGOTOMY WITHOUT DRAINAGE
SELECTIVE PROXIMAL VAGOTOMY WITH DRAINAGE
TRUNCAL VAGOTOMY ANTRECTOMY, BILLROTH I
TRUNCAL VAGOTOMY ANTRECTOMY BILLROTH II

FIG. 1. Five different operations for duodenal ulcer disease included in this study. Shaded areas denote extent of denervation.

Operative Procedures

After appropriate preoperative studies, patients were assigned randomly to the operative procedures under investigation at that time. These operations are diagrammed in Fig. 1. For purposes of this discussion, we will consider in order the three nonresective operations and then the two procedures of vagotomy and antrectomy. There was no preselection of patients within the various series except that no patient with partial outlet obstruction was assigned to selective proximal vagotomy without drainage. All operative procedures were either performed by or performed under the direct supervision of one or two members of the faculty.

The five operations were: 1) truncal vagotomy with drainage (pyloroplasty, V + P); 2) selective proximal vagotomy without drainage (SPV–D); 3) selective proximal vagotomy with drainage (SPV + D); 4) truncal vagotomy and antrectomy with gastroduodenostomy (V + BI); or 5) truncal vagotomy and antrectomy with gastrojejunostomy (V + BII). Truncal vagotomy was performed by the standard technique of division of the vagal trunks of the esophageal hiatus proximal to the point of origin of the hepatic and celiac branches. The extent of denervation effected by the various vagotomy procedures is shown in Fig. 1.

Fifteen patients were assigned to receive V + P. All but one patient had gastric drainage by the Weinberg modification of the Heinecke-Mikulicz pyloroplasty. One patient with a severe duodenal deformity underwent Finney pyloroplasty at the election of the surgeon.

Eleven patients were assigned to SPV without drainage. The object of SPV is to denervate the parietal cell area of the stomach without denervation of the antral musculature, which is the active pump mechanism for emptying the stomach. We have used a modification[34] of the technique of Goligher.[3] In this method, the anterior and posterior leaves of the gastrohepatic omentum are divided at their attachment to the stomach, from the *incisura angularis* proximally to the cardia. This severs all of the fundal branches of the descending nerves of Latarjet from the vagi, and preserves the terminal branches to the antrum (Fig. 2). Because the antral musculature remains innervated, most surgeons perform selective proximal vagotomy without drainage, but fear of gastric retention led Holle[7] to add an emptying procedure routinely. We have been engaged in a con-

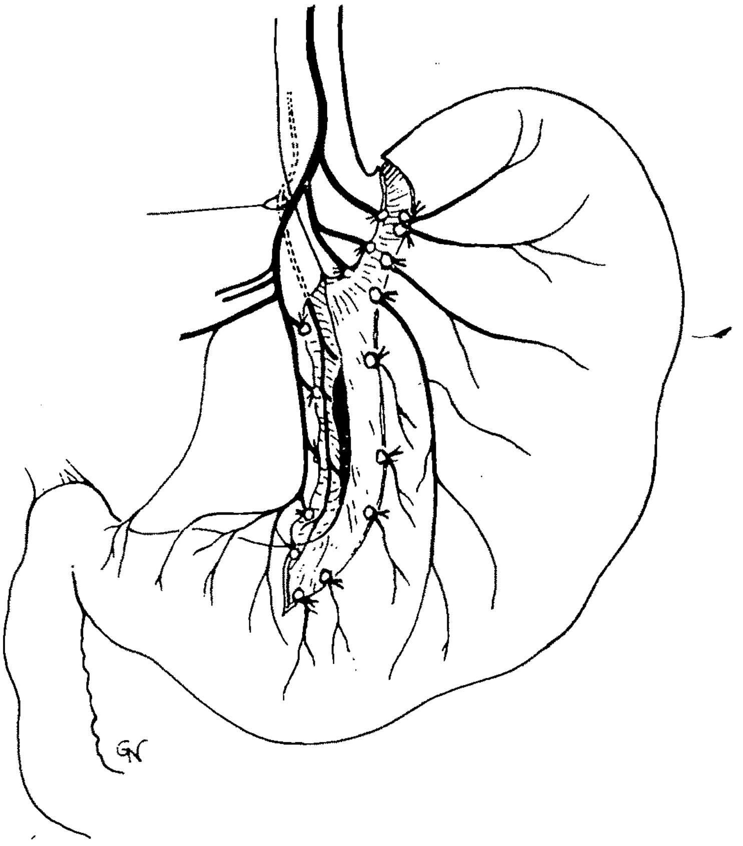

FIG. 2. Technique of selective proximal vagotomy. Fundic branches of the gastric divisions of the anterior and posterior vagi are severed along the lesser curvature and around the circumference of the fundo-esophageal junction. Antral branches of the descending vagal nerves of Latarjet are preserved.

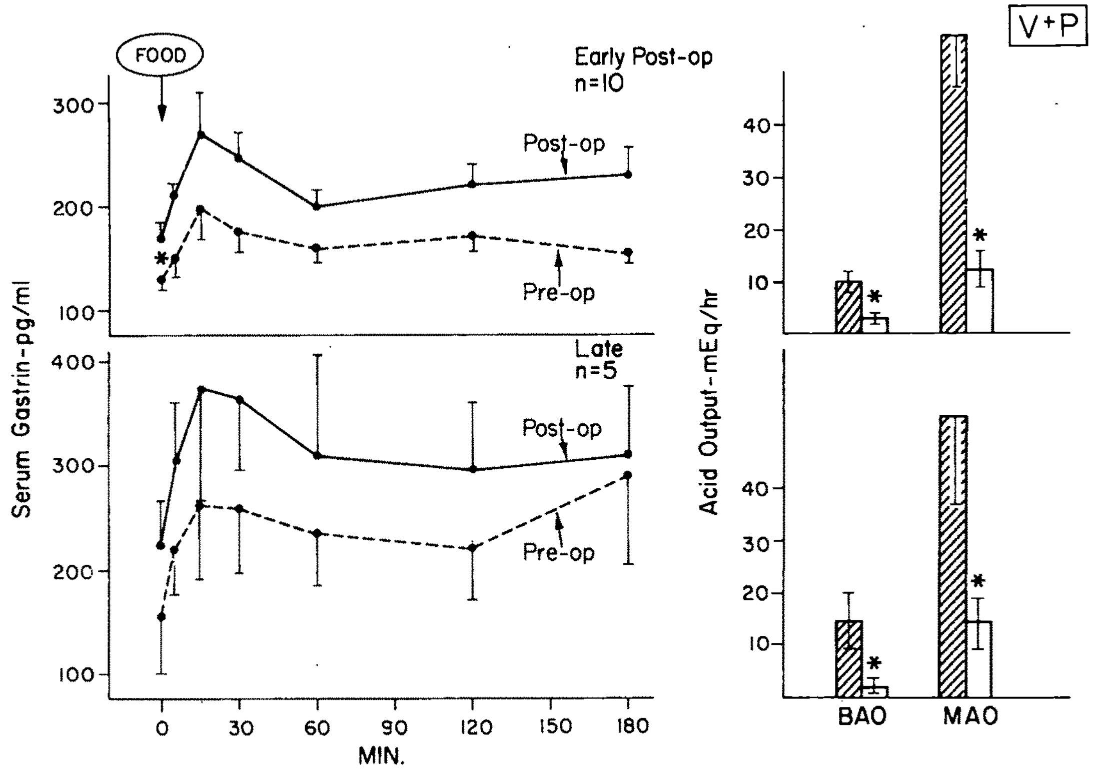

FIG. 3. Serum gastrin response to a meal and gastric acid secretion before and after truncal vagotomy and pyloroplasty. Basal acid output (BAO) and maximal acid output (MAO) after Histalog are shown on the bar graphs. The shaded bars show preoperative values and the open bars represent postoperative values. Early postoperative studies (top) were performed within 6 months of operation and late studies (bottom) were performed 6 months to 4 years after operation. Asterisks identify postoperative values that are significantly different from preoperative values.

trolled prospective random trial to test the necessity of drainage with selective proximal vagotomy.

We performed SPV with drainage in 19 patients, of whom 17 had a Weinberg modification of a Heinecke-Mikulicz pyloroplasty, one had a Finney pyloroplasty, and one had a gastroenterostomy.

Fifteen patients underwent truncal vagotomy, antrectomy, and Billroth I anastomosis. The site of proximal gastric resection was 1 cm proximal to the antrofundic junction, which is defined as a line proceeding from the *incisura angularis* inferiorly and 45° to the left, to intersect the greater curvature. The lesser curvature side of the stomach was closed in the Schoemaker fashion, and a gastroduodenostomy was performed.

Six patients underwent truncal vagotomy, antrectomy, and antecolic gastrojejunostomy.

Clinical Studies

Patients were studied before and at intervals after operation. We have arbitrarily grouped all studies performed within the first 6 months into an early group and studies performed between 6 months and 4 years into a late group. It is difficult to secure cooperation of patients for postoperative studies, and many patients failed to return for postoperative studies and are not included in this report. Forty-eight patients had early postoperative studies and 25 had late postoperative studies. Patients were admitted to the Clinical Study Center for pre- and postoperative evaluation. Postoperatively, the possibility of ulcer recurrence was routinely checked by gastroscopy and by radiography. Basal acid output (BAO) and maximal acid output (MAO) to Histalog were performed by standard techniques.[32]

We measured basal and postprandial gastrin levels before and after operation. Two fasting blood samples were obtained and the patient was then given a 250-ml liquid meal (Sustagen®) which contained 116 g carbohydrate, 44 g protein, and 5 g fat and provided 685 calories. Serial blood samples were drawn after eating and at intervals for the next 3 hours. Blood was centrifuged and the serum was stored at −20 C for subsequent measurement of gastrin by radioimmunoassay.[9,25]

Statistical Analysis

Values are expressed as the mean plus or minus the standard error of the mean (±SEM). Student's paired "t" test was used to compare differences in preoperative and postoperative data. Differences with P values less than 0.05 were considered significant. Acid reduction, in per cent, was computed for BAO and MAO for each patient, and the mean was determined by dividing the sum of the individual per cents by the number in the group.

Results

There was one operative death in the series. The patient was a 55-year-old man who underwent SPV + D for intractable pain of 20 years duration. The pyloroplasty leaked on the sixth postoperative day. The pa-

TABLE 1. *Serum Gastrin and Gastric Acid Secretion Before Operation and Within 6 Months After Operation*

		V + P	SPV − D	SPV + D	V + BI	V + BII
Gastrin (pg/ml)						
Basal	preop	130	101	99	122	81
	postop	167	120	150	142	67
	difference	↑	NS	NS	NS	NS
Postprandial	preop	198	173	140	205	121
	postop	268	243	226	215	69
	difference	NS	↑	↑	NS	↓
Acid (mEq/hr)						
BAO	preop	9.8	7.9	7.5	7.5	5.3
	postop	3.2	2.5	2.3	1.0	1.3
	difference	↓	↓	↓	↓	↓
MAO	preop	57.7	35.7	35.8	36.0	36.0
	postop	12.5	21.0	20.4	6.3	4.8
	difference	↓	↓	↓	↓	↓

The postprandial gastrin levels are all peak values, except in the V + BII group where the significantly different values at 45 minutes postprandially are given. (↑ = significant postoperative increases; ↓ = significant postoperative decrease; NS = not significant.)

tient was reoperated upon immediately, but later died of multiple intraperitoneal abscesses and hemorrhage.

Three patients have developed recurrent ulcers (proven by fiberoptic endoscopy and by radiography). Two patients in the SPV group developed recurrent ulcers within two years of operation; one patient had a drainage procedure and one did not. Both patients underwent subsequent antrectomy and truncal vagotomy and both are asymptomatic. One patient in the vagotomy and pyloroplasty group developed a recurrent ulcer. He underwent antrectomy with BI anastomosis, but recently developed a second recurrent ulcer and required further gastric resection (a cumulative resection of 85% of his stomach) plus reresection of the vagi. Serum gastrin concentrations were determined repeatedly in the three patients with recurrent ulcers. There was no evidence of the Zollinger-Ellison syndrome.

Other than recurrent ulcers, there have been no significant postoperative complications, most patients would receive an excellent or good clinical rating, and there have been no differences in the degree of patient satisfaction with the procedures.

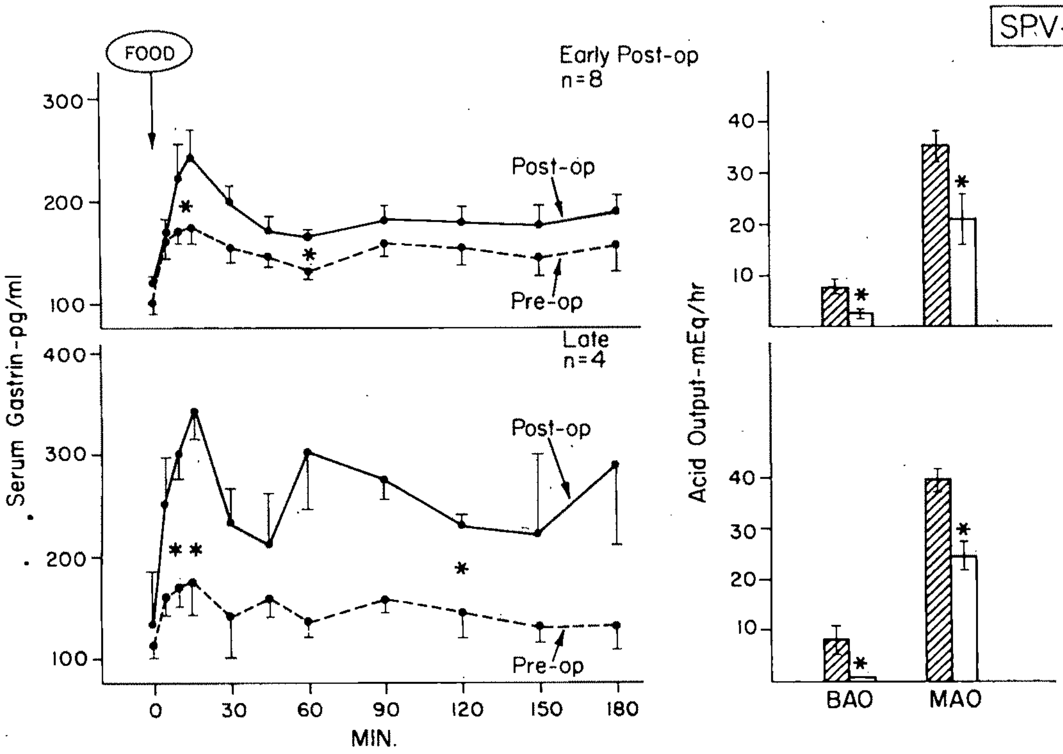

FIG. 4. Serum gastrin response to a meal and gastric acid secretion before and after selective proximal vagotomy with no drainage. Basal acid output (BAO) and maximal acid output (MAO) after Histalog are shown on the bar graphs. The shaded bars show preoperative values and the open bars represent postoperative values. Early postoperative studies (top) were performed within 6 months of operation and late studies (bottom) were performed 6 months to 4 years after operation. Asterisks identify postoperative values that are significantly different from preoperative values.

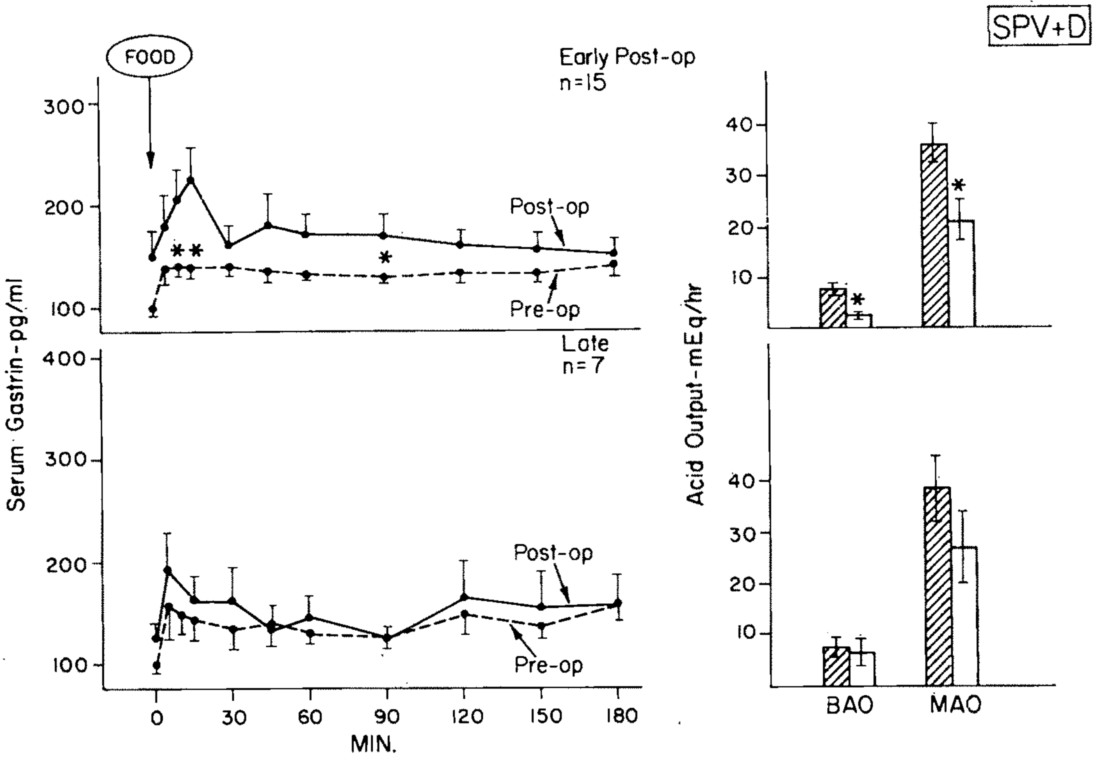

FIG. 5. Serum gastrin response to a meal and gastric acid secretion before and after selective proximal vagotomy with drainage. Basal acid output (BAO) and maximal acid output (MAO) after Histalog are shown on the bar graphs. The shaded bars show preoperative values and the open bars represent postoperative values. Early postoperative studies (top) were performed within 6 months of operation and late studies (bottom) were performed 6 months to 4 years after operation. Asterisks identify postoperative values that are significantly different from preoperative values.

We have grouped together the early (prior to 6 months) and late (6 months to 4 years) results of studies on serum gastrin and on gastric acid secretion for each of the 5 operations (Figs. 3–8). Food caused a significant increase in serum gastrin levels in each group except in patients after vagotomy, antrectomy and gastrojejunostomy (Fig. 7). Patients in the three groups receiving vagotomy without resection showed elevations of the *basal* serum gastrin after operation; the difference was significant only in the early studies on patients with V + P (Fig. 3).

Vagotomy and Pyloroplasty (Fig. 3)

There was a clear tendency for serum gastrin levels to be elevated after truncal vagotomy and pyloroplasty in both early and late studies.

Early postoperative results: The preoperative mean concentration of basal serum gastrin was 130 ± 9 pg/ml; this increased to a peak level of 198 ± 28 pg/ml 15 minutes after eating. Postoperatively, the basal level of serum gastrin was 167 ± 14 pg/ml, and this increased to a peak level of 268 ± 40 pg/ml. The basal acid output of 9.8 ± 1.9 mEq/hr decreased significantly in early studies after vagotomy and pyloroplasty to 3.2 ± 0.8 mEq/hr. The maximal acid output of 57.7 ± 9.9 mEq/hr fell to 12.4 ± 3.4 mEq/hr in early postoperative studies. Serum gastrin and acid secretory data in earyl postoperative studies after all 5 operations are summarized in Table 1.

Late: In a different group of 5 patients studied 4 years after vagotomy and pyloroplasty, the basal preoperative level of serum gastrin was 157 ± 51 pg/ml which rose to 263 ± 70 pg/ml 15 minutes after eating. Four years postoperatively, the basal serum gastrin level was 223 ± 39 pg/ml and 15 minutes after a meal, gastrin was 375 ± 110 pg/ml. Postprandial gastrin levels were uniformly but not significantly elevated over preoperative values. Preoperative acid secretory studies showed a BAO of 14.2 ± 4.8, which fell significantly to 1.7 ± 1.6 mEq/hr postoperatively. Prior to operation, the MAO was 54.5 ± 18.8 mEq/hr; this was reduced significantly after operation to 14.1 ± 5.2 mEq/hr.

Selective Proximal Vagotomy Without Drainage (Fig. 4)

Early postoperative results: The mean preoperative level of basal serum gastrin of 101 ± 11 pg/ml increased to 173 ± 17 pg/ml at 15 minutes. After operation, the mean basal level of 120 ± 6 pg/ml was elevated to 243 ± 25 pg/ml 15 minutes after eating. Postprandial levels of gastrin were significantly elevated in the postoperative studies at 15 and at 60 minutes. The BAO of 7.9 ± 1.5 mEq/hr before operation was reduced to 2.5 ± 0.8 mEq/hr after selective proximal vagotomy without drainage. The maximal acid output before operation was 35.7 ± 3.0 mEq/hr and this was diminished significantly by operation to 21 ± 5.2 mEq/hr.

Late: Although basal gastrin values were unchanged, the postprandial levels were higher in the late than in the early postoperative studies. Significant postoperative

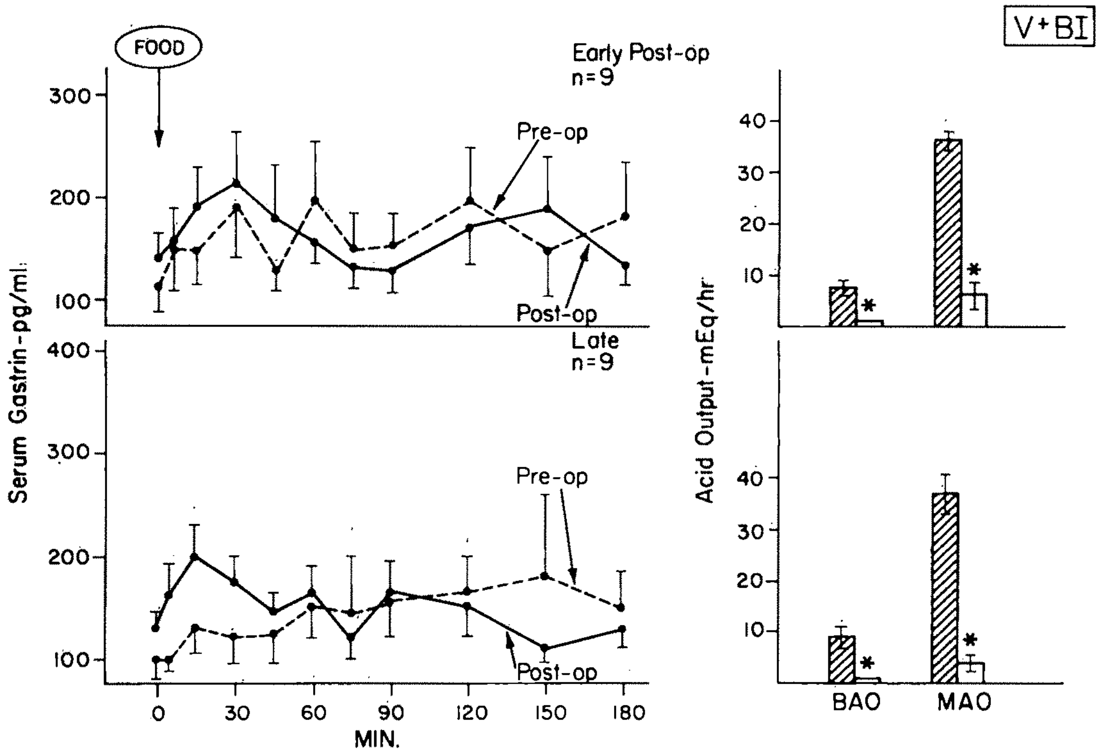

FIG. 6. Serum gastrin response to a meal and gastric acid secretion before and after truncal vagotomy, antrectomy, and gastroduodenostomy. Basal acid output (BAO) and maximal acid output (MAO) after Histalog are shown on the bar graphs. The shaded bars show preoperative values and the open bars represent postoperative values. Early postoperative studies (top) were performed within 6 months of operation and late studies (bottom) were performed 6 months to 4 years after operation. Asterisks identify postoperative values that are significantly different from preoperative values.

increases in serum gastrin were found at 10, 15, and 120 minutes. The preoperative BAO of 8.2 ± 2.8 mEq/hr was significantly reduced to 0.4 ± 0.2 mEq/hr. The MAO of 40.3 ± 2.2 mEq/hr before operation was significantly reduced in late postoperative studies to 25 ± 2.9 mEq/hr.

Selective Proximal Vagotomy Plus Drainage (Fig 5)

Early postoperative results: Serum gastrin levels were elevated at basal and postprandial periods in early postoperative studies. The preoperative basal level of 99 ± 7 pg/ml was elevated to 140 ± 11 pg/ml 10 minutes after eating. Postoperatively, the basal level of 150 ± 29 rose to 226 ± 31 pg/ml at 15 minutes. Significant postoperative differences occurred 10, 15, and 90 minutes after eating. The preoperative BAO of 7.5 ± 1.2 mEq/hr was significantly reduced to 2.3 ± 0.6 mEq/hr in the early postoperative period. The preoperative MAO of 35.8 ± 3.9 mEq/hr was diminished significantly after operation to 20.4 ± 3.9 mEq/hr.

Late: There was no significant difference between pre- and postoperative serum gastrin studies. The preoperative basal level of 101 ± 7 pg/ml rose to 159 ± 35 pg/ml 5 minutes after the meal. Postoperatively, the basal level was 121 ± 16 pg/ml which rose to 193 ± 36 pg/ml 5 minutes after eating. Neither BAO nor MAO were de-

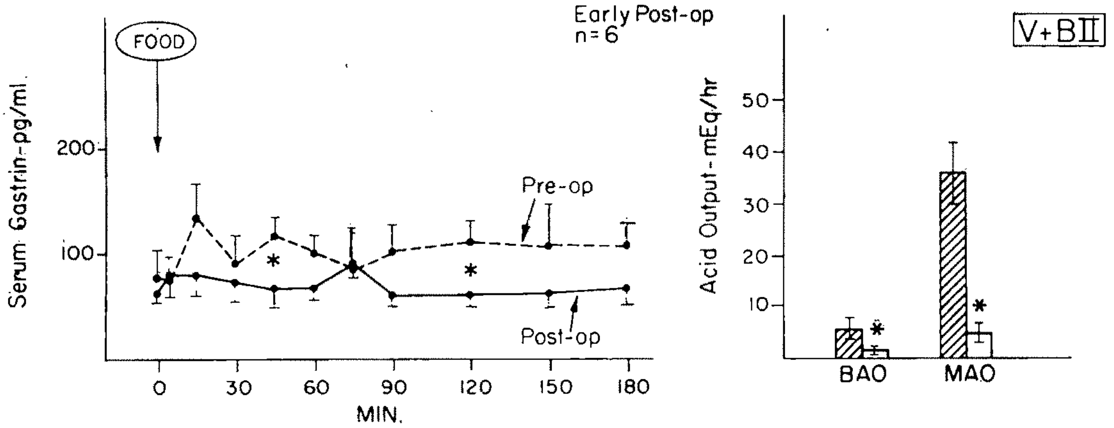

FIG. 7. Serum gastrin response to a meal and gastric acid secretion before and after truncal vagotomy, antrectomy, and gastrojejunostomy. Basal acid output (BAO) and maximal acid output (MAO) after Histalog are shown on the bar graphs. The shaded bars show preoperative values and the open bars represent postoperative values. Early postoperative studies were performed within 6 months of operation. Asterisks identify postoperative values that are significantly different from preoperative values.

creased significantly in late studies after SPV + D. Preoperatively, the BAO was 7.5 ± 1.9 mEq/hr and postoperatively was 6.7 ± 2.4 mEq/hr. The maximal acid output was 38.7 ± 6.1 and this fell to 27.3 ± 7.3 mEq/hr after operation.

Vagotomy, Antrectomy, and Gastroduodenostomy (Fig 6)

Early postoperative results: The preoperative basal level of serum gastrin was 122 ± 27 pg/ml and this rose to 193 ± 50 and to 205 ± 57 pg/ml at 30 and at 60 minutes after eating. The postoperative basal level of gastrin was 142 ± 26 pg/ml and this increased to 215 ± 50 pg/ml at 30 minutes. The serum gastrin response to food in these antrectomized patients was mobilized from extra-antral sources. The preoperative BAO of 7.5 ± 1.4 mEq/hr was diminished by operation to 1.0 ± 0.6 mEq/hr in the early postoperative period. The preoperative MAO of 36 ± 1.9 mEq/hr was reduced significantly to 6.3 ± 2.9 mEq/hr after vagotomy and antrectomy.

Late: The basal preoperative concentration of serum gastrin was 101 ± 20 pg/ml, which increased to 131 ± 25 pg/ml at 15 minutes and to 180 ± 82 pg/ml at 150 minutes. Postoperatively, the basal level of 129 ± 17 pg/ml rose to 201 ± 31 pg/ml 15 minutes after eating. The preoperative BAO was 9.0 ± 2.0 mEq/hr; this was reduced significantly by operation to 0.9 ± 0.3 mEq/hr. The preoperative MAO of 37 ± 3.8 mEq/hr was diminished significantly to 3.8 ± 1.3 mEq/hr after operation.

Vagotomy, Antrectomy, and Gastrojejunostomy (Fig 7)

Early postoperative results: The preoperative basal level of serum gastrin was 81 ± 27 pg/ml, and this rose to 138 ± 32 pg/ml at 15 minutes after food. Postoperative levels of gastrin in these antrectomized patients with a gastrojejunostomy were, for the most part, lower than preoperative values. The basal postoperative level was 67 ± 10 pg/ml, and this rose to 83 ± 18 pg/ml at 15 minutes and to 95 ± 33 pg/ml at 75 minutes after the meal. The preoperative BAO was 5.3 ± 1.8 mEq/hr and this was significantly reduced to 1.3 ± 1.0 mEq/hr postoperatively. The preoperative MAO of 36 ± 6.2 mEq/hr was reduced significantly to 4.8 ± 1.8 mEq/hr after operation.

Discussion

The purpose of this study is to report the effects of 5 operations in current use for treatment of duodenal ulcer on basal and postprandial gastrin levels and on basal and maximally-stimulated acid secretion. Results of current operations for duodenal ulcer have been recently evaluated[26,34]; we will not attempt to compare clinical results in the present series since the number of patients in each group is too small, the observation period is too short and the trials were initiated with different goals and are not comparable except in the studies on gastrin and gastric secretion.

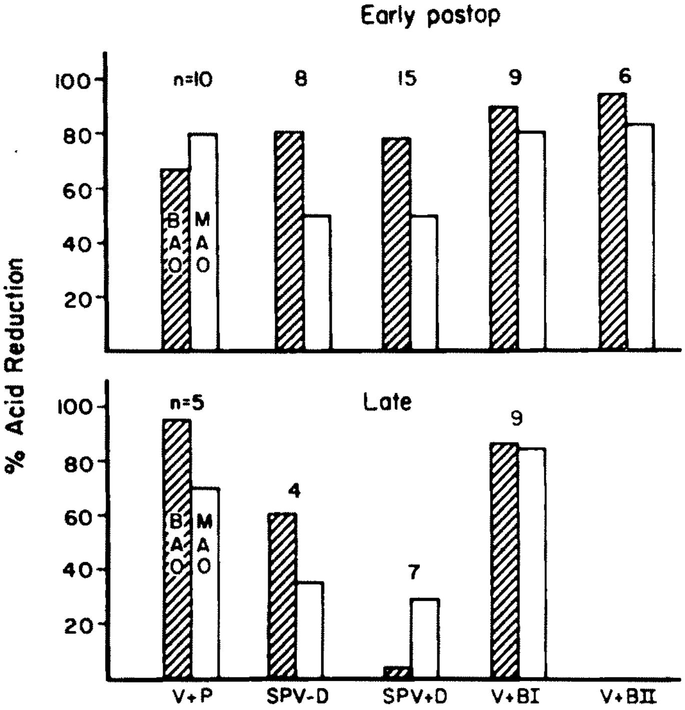

FIG. 8. Percent acid reduction after operation. Early postoperative acid studies (top) were performed within 6 months of operation; late acid studies (bottom) were performed 6 months to 4 years after operation. Basal acid output (BAO) is shown by the shaded bars; maximal acid output (MAO) is shown by the open bars. The number of patients in each group is shown above the bars.

In the groups of patients reported, vagotomy without resection caused an increase in serum gastrin values. Antrectomy caused a decrease in gastrin values in patients with gastrojejunostomy and no change in patients with a gastroduodenostomy. Acid secretion was reliably reduced by all operations (the greatest reduction was with vagotomy and antrectomy and the least with selective proximal vagotomy). Early changes in gastrin and acid levels after selective proximal vagotomy were not influenced by drainage but in late studies, drainage was associated with loss of postoperative elevation of gastrin levels and diminished reduction of acidity.

There are several possible effects of vagotomy on the physiologic release of gastrin. At least two are predictable. There may be an increase in basal and postprandial levels of gastrin because of loss of acid inhibition, or there may be a decrease in basal and postprandial levels because of loss of vagal release of gastrin. The present study, as well as others,[1,31,35] indicates that in man the first option clearly predominates. Other possible (but less likely) causes of increased levels of gastrin after vagotomy are mobilization of extragastric gastrin, whose release might be inhibited by the vagus,[6,15] or loss of vagally controlled inhibition of antral gastrin release.[2] Postoperative increases in serum gastrin levels have been reported after all forms of vagotomy[33] (truncal vagotomy,[1,2,24,31] selective gastric vagotomy[11,16] or selective proximal vagotomy[10,11,18,19,28,34]). In early postoperative studies[18,34] there was no difference in gastrin release in patients with selective proximal vagotomy with and without drainage operations. Recent clinical studies have suggested that vagal release of antral gastrin plays only a minor role, if any, in the typical gastrin response to food,[28] and even the release of gastrin by insulin, apparently, does not depend entirely on the vagus.[27] Comparison of the slopes of the postprandial gastrin curves in Figs. 3, 4 and 5 reveals that postoperative patients have a rapid increase in serum gastrin after eating, a rate of increase that does not differ from the preoperative curve. This comparison provides further evidence that the vagus is not an important factor in food-stimulated release of gastrin in man.

The normal appearance of the postprandial gastrin response to V + BI patients (Fig. 6) and not in V + BII patients (Fig. 7) confirms previous reports that patients after antrectomy with gastroduodenostomy show postprandial release of duodenal gastrin[1,17,31] and patients after gastrojejunostomy do not.[31] The shape of the early postprandial gastrin curve in post-V + BI patients (Fig. 6), suggests that mechanisms for release of duodenal gastrin operate rapidly and are independent of the vagus.

A comparison of the percentage reduction of BAO and MAO after the different operations is shown in Fig. 8. Although many series designed to compare results of various acid-reducing operations for duodenal ulcer have suggested that the degree of acid reduction achieved by most procedures is comparable,[8,13,14] our results suggest that selective proximal vagotomy does not achieve the same degree of acid reduction as do other methods and that with time, this difference is accentuated (Fig. 8). The degree of reduction in BAO and MAO after vagotomy and pyloroplasty (especially in late studies) is larger than that usually reported; we can only ascribe this difference to chance.

Although Johnston and colleagues[4,23] have suggested that the reduction in peak acid output seen one year after proximal selective vagotomy is unchanged over the next four years, they report an incidence of positive secretory responses to insulin of 80–90% at 4 years in spite of an early incidence of only 3%.[12] Return of acid secretion, with time, after operation leads to apprehension of a high recurrence rate. In spite of the high incidence of positive insulin response at 4 years, Johnston[12] claims that not one of 400 patients followed up to 5½ years has a proven recurrent ulcer. Kronborg and Madsen[22] reported an incidence of recurrent ulceration after selective proximal vagotomy of 22% in a series of patients followed from one to 4 years.

We have used the insulin-stimulatory test (Hollander) in the past, but we are not using it routinely now. The reasons for this change in attitude have been clearly summarized by Grossman[5]; secretory tests are of little value in diagnosing recurrent ulcer, insulin tests are no better than other secretory tests in separating patients with recurrence from those without recurrence,[21] and the notion that insulin-stimulated acid secretion is mediated only by the vagus is unproven. Since antrectomy alone may result in a negative Hollander test,[20,30] the entire anatomic significance of insulin testing must be reassessed. Although insulin tests probably detect most incomplete vagotomies, as few as 60% of patients with recurrent ulcer have a positive response; 10% of patients with positive Hollander tests and 2% of patients with negative Hollander tests develop recurrence.[26] Because the insulin test is difficult to interpret and is dangerous,[29] and because it provides no better discrimination than any other secretory test, we have replaced it with determination of maximal acid output by Histalog or pentagastrin.

Lastly, there appears to be no predictive value of either serum gastrin levels or acid secretory values for ulcer recurrence in an individual patient. We carefully studied the 3 patients in our series with recurrences and their gastrin and acid values, taken either alone or in comparison with their preoperative values, are no different from those of their peers.

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DISCUSSION

DR. H. WILLIAM SCOTT, JR. (Nashville): Dr. Fritz Holle of Munich has been very much interested for many years in using selective proximal vagotomy in patients with duodenal ulcer, and he has observed hypergastrinemia in patients in whom a complementary drainage procedure has not been used. However, he maintains that when one does an appropriate pyloroplasty, that accomplishes drainage of the antrum; the hypergastrinemia is eliminated. This should be somewhat analogous to the Billroth I anastomosis, after similar vagotomy and antral resection. And I don't understand why Dr. Thompson's results are so divergent to those of Dr. Holle.

Dr. Holle worries greatly about the possibility of recurrence of ulcer after selective proximal vagotomy and no drainage, and for this reason warns against use of the operation. He, of course, is greatly opposed by Gallagher, Johnston, and others in this country. I hope Dr. Thompson will explain this for us.

DR. CLAUDE E. WELCH (Boston): We have heard some comments this morning about the difficulties with clinical impressions. We need quantitative measurements to replace clinical impressions. For example, some of us old-timers believe that duodenal ulcer diathesis is becoming a little less virulent than it was years ago. Dr. Thompson now has a method by which he might be able to quantitate some of the agents that cause ulcer, and may be able to tell us in the years to come whether the disease actually has changed or not.

DR. FRANCIS C. NANCE (New Orleans): I really have only one question to ask, and that is why the gastrin levels are not further elevated in the patients with selective vagotomy and drainage, and no drainage, with the continued preservation of innervation of the antrum. I would have expected far higher stimulation of gastrin release.

DR. SAMUEL R. POWERS (Albany, New York): According to the diagram that you showed about the production of acid, I would not have expected that proximal gastric vagotomy would alter the response to food very much, because it primarily interrupts the cephalic phase. My question is: Does the fact that it does not appreciably alter the response to food mean that this is an indictment of the operation, or is, perhaps, this one of its benefits?

The second question related to the point that Gallagher and others have made; namely, that, although there has often been a return of acid production, there apparently has not been a return of the ulcer. Have you any data on the recurrence of ulcer in these patients where the acid secretion did recur?

DR. THOMAS BOMBECK (Chicago): I would like to ask one question, and it's a little esoteric, but it gets at just that problem. Dr. Thompson has shown that, although gastrin increases following parietal cell vagotomy, acid secretion decreases.

Now, it's tempting to speculate that this may be due to denervation of the parietal cell, but there is one other explanation, and I'm sure he's capable of measuring it. That is: Does vagotomy of the antrum, or preservation of vagal innervation to the antrum, in this particular situation, in any way alter the species of gastrin which is released? A change in biological activity of the gastrin which is released would explain all these findings. And does he have any evidence about that?

DR. JAMES C. THOMPSON (Closing discussion): The obvious beauty of selective proximal vagotomy is that we're able to affect the ulcer diathesis without opening the lumen of the gut. Since almost all complications of enteric surgery have to do with making openings in the gut, and their failure to close, that's a significant advance. I think that if you are going to have to do an emptying procedure, you really lose, Dr. Scott, all of the advantages of this procedure.

If you are going to have to do an emptying procedure, I really don't think that it's going to be any better than truncal vagotomy and an emptying procedure. In fact, I think that's what Dr. Kay has been saying for some time now, that since we really have a pretty good operation—in fact, we have two very good operations for duodenal ulcer disease; truncal vagotomy and pyloroplasty, or gastroenterostomy and truncal vagotomy and antrectomy—that any new advance is going to have to be absolutely first-rate in order to make it worth our time.

I would like to say, Dr. Welch, that in all of our studies the only relationship we have found between gastrin and the ulcer diathesis actually is in Zollinger-Ellison patients. We have not found there to be any predictive value whatsoever between gastrin levels and the severity of the ulcer diathesis, the possibility of recurrence, or even in retrospective studies, to go back and study the patients who have recurred. Their gastrin levels are no different than their nonrecurrent peers.

I must say, that's also true for acid production. There are no predictive values in either one of these for an individual. I'm sure that if we were to gather together 200 or 300 patients with recurrences, that acid levels would tend to be higher; but that's not any help for any single individual.

I'd like to show a slide that will partially answer the questions of Dr. Powers and Dr. Nance. They were enigmatic questions, and I'll try to give an enigmatic answer.

(Slide) Now, this is interesting. I think that it's important to know that when you do a vagotomy, there are two possible effects that you might predict on gastrin levels, and they are opposite from one another. First of all, you might suspect that there would be a decreased acid production following vagotomy, and that this would end up causing a diminished acid inhibition of gastrin release, with resultant increase in serum gastrin levels.

The other possibility is a loss of vagal activity would cause a loss of vagal release of gastrin, leading to a diminished serum concentration of gastrin. The consistent increases in serum gastrin levels after vagotomy indicate that the first option—that is, increase in serum gastrin levels due to loss of acid inhibition—clearly predominates. And that is seen in every kind of vagotomy procedure that is done, without resection.

Another clue that the vagal release of gastrin may not be important in man may be obtained by comparing the preoperative and postoperative slopes on the gastrin curves in the first fifteen minutes after food. That is the period in which the vagal factors are supposed to be most operative—in the period of stimulation of vagal release by sight or smell of food. There is no difference in the shapes of these two curves, despite the fact that in one group of patients the patient has a vagus intact, and in the other one he does not.

There is no hold-up in the rate of gastrin release in vagotomized patients. Therefore, vagal control of gastrin release must not be a major factor in man.

Dr. Bombeck asked: Does preservation of the nerves to the antrum result in any changes in molecular species? Or, in fact, do vagotomies of any type result in changes in molecular species?

This is an interesting question, and we have been trying to solve it for some time. Gastrin exists in at least ten molecular sizes, about four of which are probably inactive, and six of which are active. Obviously, if there was a predominance of inactive forms, you might get a rise in total amount of gastrin without concomitant rise in biologic activity.

We have been somewhat mesmerized by the possibility that gastrin is involved in duodenal ulcer disease for a long time, because it's really annoying to spend your life studying a hormone, and then find out that it may have little to do with the ulcer diathesis.

I'm not completely discouraged. You know, Dr. Charles Code has been mining the histamine field for almost 35 years, and now the role of histamine in gastric secretion appears to be firmly established.

Book Reviews

Pediatric Surgical Pathology. Louis P. Dehner, M.D., St. Louis, C. V. Mosby Co., 1975.

PEDIATRIC SURGICAL PATHOLOGY by Louis P. Dehner is a scholarly and significant contribution to the study of diseases of infancy and childhood. The structure of this work, bound attractively in red, lends itself to use by learners at all levels both as a textbook and up-to-date reference source. Subject matter is dealt with by organ system, and the book's 823 illustrations are appropriate, clear, and generally of high quality. Throughout each chapter careful attention has been given to clinicopathologic correlation, and characteristic clinical and pathologic findings are displayed clearly in over 68 tables and charts to the reader's benefit. The chapter dealing with renal diseases contains 11 electron micrographs displaying those ultrastructural features which clinicians and pathologists must rely upon in modern nephrology. Possibly helpful would be the inclusion of several microphotographs of immunofluorescent patterns characteristic of glomerulopathies commonly seen in childhood. The chapter dealing with bone and joint disease is an excellent synthesis of radiologic and light microscopic features of tumors, and tumor-like lesions. As such, it underscores the interdependence of radiology, pathology, and clinical medicine in diagnosis.

In summary, this careful and complete work dealing with the specialized area of pediatric surgical pathology will find broad usage by all students of medicine.

WILLIAM D. BRADFORD, M.D.

Year Book of Urology, 1975. J. T. Grayhack, Editor, 383 pages. Chicago, Year Book Medical Publishers, 1975, $18.50.

THE 1975 EDITION of the *Year Book of Urology* joins in celebration of the seventy-fifth anniversary of the ubiquitous *Year Book* series. As a separate entity, the *Year Book of Urology* has enjoyed great success since 1933, due in the largest part to the diligent and critical efforts of its four successive editors, John H. Cunningham of Harvard, Oswald Lowsley of Cornell, W. W. Scott of Hopkins, and—since 1963—John T. Grayhack of Northwestern.

The current edition meets the same high standards which have been achieved over the years. Consisting of 362 pages plus subject and author indices, the volume includes summaries and critical editorial comments on selected contributions to the urologic literature. All phases of urology are included, ranging from diagnostic advances to surgical technique and embracing the entire genitourinary system from the adrenal gland to the external urethral meatus.

Of particular value are the summaries of articles from the foreign or non-urologic literature, often escaping attention of American urologists. Abstracts are presented with succinct clarity, and the interspersed editorial comments by Grayhack and his collaborating colleagues —William H. Boyce, Frank Hinman, Jr., and Lowell R. King—offer valuable insight and perspective.

The *Year Book of Urology* is highly recommended as a convenient and satisfactory method of reviewing pertinent urologic advances of the year just passed.

JAMES F. GLENN, M.D.

Year Book of Surgery, 1975. Seymour I. Schwartz, Editor, 521 pages. Chicago, Year Book Medical Publishers, 1975, $19.25.

THIS MARKS the 75th anniversary of the publication of the *Year Book* Series. The concept was originated in 1900 by a Chicago physician, Gustavus P. Head, who recognized the need for a series of publications to update recent contributions in both a selective and authoritative manner. The *1975 Year Book of Surgery* continues in the best of tradition and is outstanding in all respects.

In reviewing this admirable text, one is impressed both by the choice of papers which are summarized as well as the editorial comments which follow each presentation. The volume begins with what is entitled the "Annual Overview" in which the major contributions to surgery for the past year are concisely described. Following the overview, 26 specific areas in the disciplines of surgery are separately reviewed. The major strength of this text is the high quality and respected stature of the members of the Editorial Board. Each is an authority in his field and the critiques which follow the abstracts are soundly based, both from point of view of clinical judgment as well as research implications.

Once again the high standards set by the *Year Book of Surgery* have been achieved in the 1975 edition. It can be recommended to all surgeons with enthusiasm.

DAVID C. SABISTON, JR., M.D.

Plastic Surgery. Tord Skoog, 500 pages. Philadelphia, W. B. Saunders, 1975, $120.00.

THIS IS A BEAUTIFULLY ILLUSTRATED compendium of Tord Skogg's contribution to Plastic Surgery. It is succinctly described by the author in the preface as a culmination of thirty years' work.

The book does not cover the entire spectrum of plastic surgery but rather, the material is restricted to the philosophies, innovations, and surgical techniques that are largely those of the author's. An abundance of meticulously accurate and informative illustrations complete the publication.

For the student of plastic surgery, this book is extremely deficient. It lacks completeness, but does elaborate on those areas of plastic surgery in which the author has been most interested through the years.

The first section of the book dealing with cleft lip and palate is a well documented presentation of Skoog's theories as well as his experimental and clinical results. The latter part of the book tells "how I do it" in relation to a few specific areas of plastic surgery. Throughout the book are subtle advertisements by manufacturers of surgical materials which are inappropriate in this type of publication.

This book should not be interpreted as a textbook of plastic surgery but a beautifully illustrated summary of a well respected plastic surgeon's ideas and techniques. This book will not appeal to the average plastic and reconstructive or general surgeon because of its limited scope, devoid of alternate planning techniques. Also, the cost is a significant deterrent.

CALVIN R. PETERS, M.D.

Management of Trauma: Pitfalls and Practice. A. J. Walt and R. F. Wilson, 626 pages. Philadelphia, Lea & Febiger, 1975, $30.00.

THIS BOOK ON TRAUMA is very timely considering the nationwide interest on "The Neglected Epidemic." The authors have presented a broad approach to trauma management and have used a rather innovative technique in the book. Interspersed throughout the text in bold type are axioms and pitfalls of trauma care. Although not everybody will agree 100% with these "pearls of wisdom" they do represent the concepts of a very large and respected trauma center.

A particularly strong chapter is the first which deals with organization of the emergency department. The section on specific injuries also has considerable valuable information. The authors stress the value of having a "captain of the ship" in caring for trauma victims in the critical care unit and this cannot be over-emphasized.

Criticisms of the book should not be interpreted as such but more as suggestions for future editions. Shock is defined by the authors as poor or inadequate cell metabolism, yet the remainder of the chapter addresses itself primarily to extracellular physiology. The investigations of Mela and Baue are not discussed. The chapter on metabolism and nutrition should be more detailed and the chapter on disaster planning should include natural disasters, such as earthquakes and hurricanes. Finally, the authors have not solved the dilemma as for whom the book should be intended. Should it be broad and general for the emergency department physician or should it be more comprehensive and detailed for the traumatologist?

DR. DONALD TRUNKEY

Circulatory Physiology II: Dynamics and Control of Body Fluid. Arthur C. Guyton, A. F. Taylor and H. J. Granger, 397 pages. Philadelphia, W. B. Saunders Co., 1975, $20.00.

THIS MONOGRAPH is the second in a series on circulatory physiology which Arthur C. Guyton has written in an attempt to fuse modern physiology with current medical practice. The first volume entitled "*Cardiac Output and Its Regulation*" was published in 1963 and a second edition appeared in 1973. Subsequent volumes are planned on arterial pressure and hypertension and another on the systems analysis approach to quantitative and computer analysis of the circulation.

The contents of the monograph include sections on extracellular, intracellular and interstitial fluids, determination of different types of tissue pressures, capillary exchange and normal fluid convection in the interstitial spaces, the lymphatic system, automatic intrinsic regulation of protein pressures and volume in the interstitial fluids, pulmonary interstitial fluid and its dynamics, pulmonary edema, and renal, neural and endocrine mechanisms for the control of body fluid volumes. An outstanding feature of the text is its concise and highly understandable language. Complicated physiological processes are made clear and the various sections interrelate quite well one to another.

After reading this excellent monograph, one is convinced that the authors' intent to correlate basic and clinical science has been achieved. This text represents a fine addition for all clinicians who seek basic explanations for a variety of physiological processes involved in the dynamics and control of body fluids. It is an especially useful reference source for students and teachers, and it has much practical value for those engaged in clinical surgery.

On the basis of the first two monographs, which the distinguished senior author has written in this series on circulatory physiology, the additional ones being planned will be awaited with considerable anticipation.

DAVID C. SABISTON, JR., M.D.

Urologic Surgery (2nd edition). James F. Glenn and William H. Boyce, 1018 pages. Hagerstown, Md., Harper & Row, 1975, $65.00.

DR. JAMES F. GLENN has recently edited the second edition of "Urologic Surgery" published by Harper and

Row. This is a greatly expanded textbook of urological surgical procedures in one volume, and both the scientific scope of the book and the number of procedures mentioned have been increased. There are now some 71 contributing authors and members of the Editorial Board who have contributed to the increased appeal to the practicing urologists and the residents. Entirely new sections have been added whereas others have been broken down into smaller units or chapters to give varied input from specialists who have contributed most to the respective subject matter.

For instance, there is an entirely new section on Urethral Stricture by Richard Turner-Warwick which is a very complete and thorough discussion of the surgical management of urethral strictures. Unfortunately, he gives very little mention of one of the most promising means of surgically treating the urethral stricture; that being the full thickness free skin graft technique.

Other new and excellent contributions are chapters on the treatment of priapism, lower urinary tract trauma, renal trauma, pelvic lymphadenectomy, urethral valves and surgery of infertility, to mention but a few. Unfortunately, in expanding the contributors to the text, there has been repetition of subject matter in various chapters, and one must be careful to use the index in looking up subject matter, rather than going strictly by the Table of Contents. For instance, Dr. C. D. Clevey's excellent chapter on Operations on the Penis and Urethra has been supplemented by a chapter on Hyperspadias by Norman B. Hodson, M.D. It is quite apparent that a considerable effort has been made to increase the appeal for this book to those doing Pediatric Urologic surgery, and it does supplement the existing literature in this field in an excellent fashion.

William Brannen, M.D.

Gastrointestinal Hormones: A Symposium. Edited by James C. Thompson, M.D., 666 pages. Austin, University of Texas Press, 1975, $15.00.

This is a superb compendium of the papers presented at a timely Symposium on Gastrointestinal Hormones held at the University of Texas Medical Branch, Galveston, in October of 1974. The contributors include all of those who have made significant advances in this important field and the volume represents an up-to-date compilation of the latest knowledge which has been gleaned from basic investigations in the field. Although most of the papers are concerned with very basic scientific studies, many items of clinical interest are also presented. Therefore the book will be an important reference mainly for those actively working in the field although clinicians will be particularly attracted to the chapters by Strauss and Yalow on the differential diagnosis of hypergastrinemia, that by Lars Olbe on gastrin release in man, and the contribution by Bloom and Polak on the role of VIP in pancreatic cholera. Despite the multiplicity of authors, the chapters are of uniformly high quality and contain much in the way of new and valuable information. The figures and tables are clearly elucidated and well chosen to illustrate important points. The references are pertinent and up-to-date. This superb volume is highly recommended to anyone interested in the latest information available in the field of gastrointestinal hormones.

Dr. William Silen

Surgical Disorders of the Adrenal Gland: Physiologic Background and Treatment. Harrison, Gann, Edis and Egdahl. 150 pages. New York, Grune & Stratton, Inc., 1975, $14.50.

A refreshing approach to a better understanding of the functioning of the adrenals in health and disease pervades this volume throughout. An experience by the 4 authors with patients and their surgical disorders of the adrenal gland that includes their basic research and its results in clinical care provides a widening horizon.

Anatomy, physiology and pathology are brought together by historical background of past centuries that emphasizes the rapid and continuing progress in this area of endeavor over the past 50 years. The significance of the physiologist, Waltern Cannon, upon this development is well presented. The authors have extended this in the much wider problems of shock and vascular collapse occurring in the wake of trauma and infection.

The clinical presentations and correlations with laboratory investigations are models for those who have these facilities. The solution of problems that are encountered in patient care is the direct method of advancement. This has been the trend followed by many engaged in pursuing the disorders of the adrenals that are now allayed or cured by surgery.

Perhaps an additional overall evaluation of the approaches of others and their results in the clinical management of the diseases discussed would be relished by the readers. Specifically this is applicable to the extra-adrenal catecholamine synthesizing tumors such as those arising from the organs of Zuckerkandl.

Surgeons and those involved in endocrinology should gain the most from this monograph. It has great potential for medical students and may inspire lasting interests.

Dr. Frank Glenn

Atlas of Surgical Operations (4th edition). Robert M. Zollinger and Robert M. Zollinger, Jr., New York, McMillan Publishing Company, Inc.

The fourth edition of "*Atlas of Surgical Operations*," which has just become available, combines the two volumes of the third edition in one complete volume. The return to a single volume will certainly increase the convenience and usefulness of this Atlas.

As in the previous edition, the superb illustrations are reproduced with a striking clarity of detail permitting the pertinent accompanying text to appear on the opposite page. Here, with each surgical procedure illustrated, is a brief section covering the indications for operation, choice of anesthetics, and pre and postoperative care.

It is a Herculean task to present in one volume of 392 pages the pertinent data on those surgical procedures coming within the accepted scope of the general surgeon. In this, the authors have succeeded eminently for the text carries out the high tradition of its predecessors. Initially designed to aid the inexperienced, younger surgeon, the Atlas continues to do this but provides the older general surgeon, working often far removed from a medical center, with a rich source of reference.

This Atlas bears the unmistakable stamp of its distinguished author, now so ably joined by a gifted son. This union promises a continuity of authorship in future years.

C. W. McLaughlin, Jr., M.D.

Transplantation Today, Vol. III. Schlesinger, Billingham and Rapaport, 922 pages. New York, Grune & Stratton, Inc., 1975, $37.50.

This volume contains the papers presented at the Fifth International Congress of the Transplantation Society, August 1974, in Jerusalem, Israel. While the material is diverse, it is well organized and categorized into appropriate sections. These include histocompatibility genes, cell membrane antigens, effector mechanisms, tolerance and enhancement, tumor immunology, organ preservation, clinical and experimental organ transplantation, bone-marrow transplantation, and the reports from seventeen workshops.

There are 206 separate papers and, as might be expected, the contents are somewhat uneven, but the editing is superb. The reports are a concise three to six pages in length, cogent and clear. The inevitable abbreviations are abundantly used, but aside from that, the text is quite readable.

The clinician who does not work on a continuing basis with, for instance, transplantation genetics, may be mystified with the jargon, models and data base that the authors take for granted. The subject matter covered in this book is undergoing continuous change and it is associated with an expanding vocabulary of highly technical terms. Aid to the uninitiated is offered via a summary statement by an authority for each section.

Despite the time lapse since the conference, the material is generally pertinent and timely. The text is useful as a survey and as a reference of the current research and clinical activity in the field of transplantation immunology.

Jay Collie Fish, M.D.

Techniques of Clinical Gastroenterology. H. W. Boyce, Jr. and E. D. Palmer, 487 pages. Springfield, Charles C Thomas, 1975, $28.50.

Drs. Boyce and Palmer have written a readable, lucid text describing all of the common (as well as many uncommon) techniques employed in clinical gastroenterology. The material is organized into five sections: gastrointestinal endoscopy, treatment of esophageal obstruction, biopsy techniques, and transabdominal needle aspiration techniques. The recent ascendancy of diagnostic and therapeutic endoscopy is highlighted with excellent and highly practical chapters describing current equipment, as well as safe use and care of the equipment. It is clear that the development of safe effective endoscopic procedures has been the most important recent advance in the care of patients with gastrointestinal disease. Section II dealing with treatment of esophageal obstruction is similarly well written but will unlikely uncover differences in opinion regarding treatment of esophageal obstruction. Although carcinoma of the esophagus is a highly lethal disease regardless of treatment employed, the enthusiasm for dilatation of carcinoma of the esophagus described in the text will be of interest to surgeons. The section on biopsy techniques includes 18 chapters on various biopsy methods of liver, stomach, and intestine as well as various secretory and motility studies. The use of balloon tamponade for the control of bleeding esophogogastric varices was especially good and should be required reading for all novices as well as those with experience with this problem.

The last section on transabdominal needle aspiration techniques in the reviewer's opinion was the weakest of the sections. Information is available to permit better definition of indications for peritoneal tap as well as better interpretation of results than described by the authors. The reader is left with the impression that taps should be done in all cases "when there is poorly understood acute abdominal pain." Many clinicians would disagree with this opinion. Some of the methods suggested for measuring portal venous pressure are tried and true however, some such as needling an esophageal varix during esophagoscopy we will observe with great interest.

This book is complete, well written, and thorough. Above all it is practical providing information which will be transformed promptly into improved patient care and that is an admirable goal for any medical text.

Techniques of Clinical Gastroenterology should be in every Medical and Surgical Department Library for student, staff, and housestaff. This book deserves our most enthusiastic recommendation.

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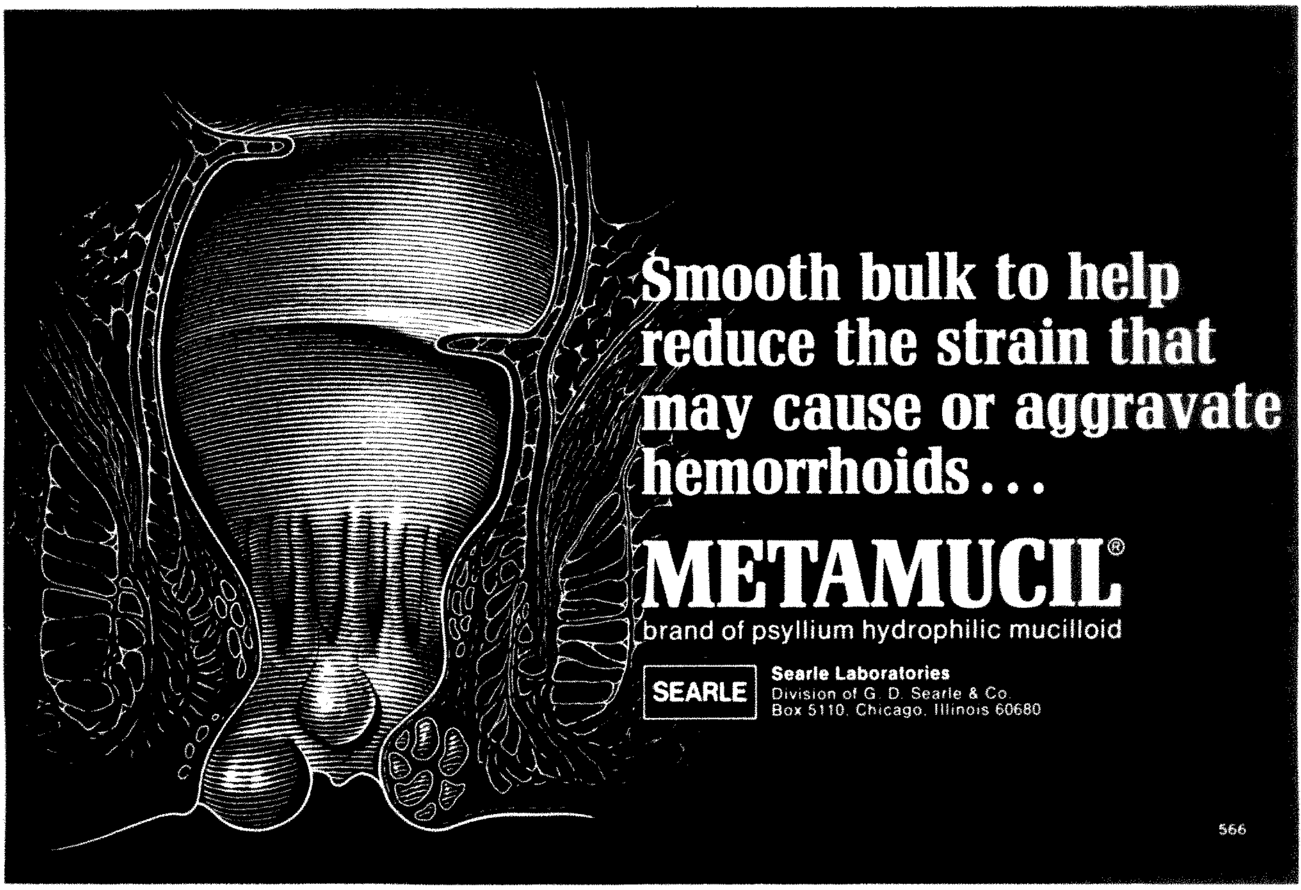
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Warnings: Phenothiazines are capable of potentiating CNS depressants as well as atropine and phosphorous insecticides. The drug may impair mental and/or physical ability required in the performance of potentially hazardous tasks such as driving a car or operating machinery.

Postoperative Nausea and Vomiting: When used to control postoperative nausea and vomiting in patients undergoing elective surgical procedures, restlessness and postoperative CNS depression during anesthesia recovery may occur. Possible postoperative complications of a severe degree of any of the known reactions of this class of drug must be considered. Postural hypotension may occur after an initial injection, rarely with the tablet or suppository. Do not use with epinephrine in the treatment of drug-induced hypotension as phenothiazines may induce a reversed epinephrine effect. The most suitable vasoconstrictor agents are levarterenol and phenylephrine. The use of Torecan has not been studied following intracardiac and intracranial surgery. Not recommended for use in children under 12 years of age, or in nursing mothers since safety and efficacy have not been established.

Precautions: Convulsions and abnormal movements such as extrapyramidal symptoms have occurred. The varied extrapyramidal symptom complex is more likely to occur in young adults and children. Extrapyramidal effects must be treated by reduction of dosage or cessation of medication. For treatment of nausea and/or vomiting associated with anesthesia and surgery, the drug should be administered by deep intramuscular injection at or shortly before the termination of anesthesia.

Adverse Reactions: CNS: convulsions, extrapyramidal symptoms such as dystonia, torticollis, oculogyric crisis, akathisia and gait disturbances, occasional cases of dizziness, headache, fever and restlessness have been reported. Drowsiness may occur initially on injection but is usually alleviated by a reduction in dosage. Dryness of the mouth and nose, blurred vision, tinnitus; sialorrhea and altered gustatory sensation. Peripheral edema of the arms, hands and face. Cholestatic jaundice; cerebral vascular spasm and trigeminal neuralgia have been reported occasionally. The following have occurred with phenothiazine derivatives and should be considered: agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia, pancytopenia, eosinophilia, leukocytosis; miosis, obstipation, anorexia, paralytic ileus; erythema, exfoliative dermatitis and contact dermatitis; jaundice, biliary stasis. Hypotension, rarely leading to cardiac arrest; ECG changes. Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia, some of which have persisted for several months or years especially in patients of advanced age with brain damage. Menstrual irregularities, altered libido, gynecomastia, weight gain; false positive pregnancy tests. Urinary retention, incontinence; fever, laryngeal edema and angioneurotic edema, asthm Hyperpyrexia, behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses and toxic confusional states. ECG changes. While there is no evidence that ECG changes are in any way precursors of any significant disturbance of cardiac rhythm, sudden and unexpected deaths apparently due to cardiac arrest have been reported in a few instances in hospitalized psychotic patients previously showing characteristic ECG changes. A peculiar skin-eye syndrome, which is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea, has also been recognized as a side effect following long-term treatment. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported.

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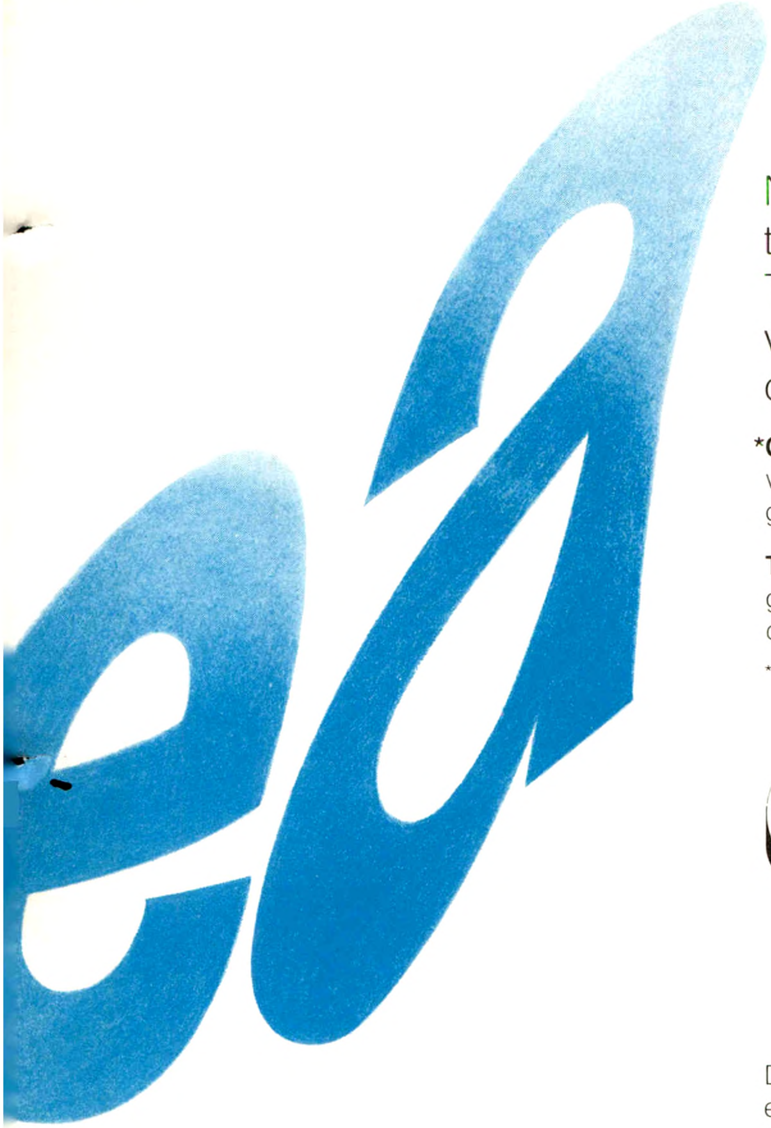
For complete details, please see full prescribing information.



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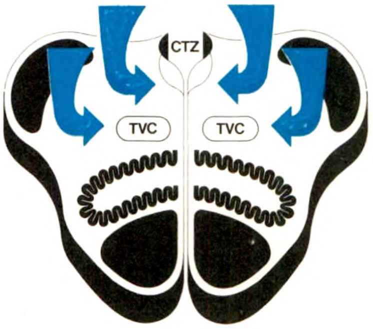

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The general effectiveness of Nebcin is now well known. Clinical studies have shown Nebcin to be indicated in the treatment of septicemia; C.N.S. infections, including meningitis; neonatal sepsis; serious lower respiratory infections; gastrointestinal infections, including peritonitis; skin, bone, and soft-tissue infections, including burns; and serious complicated and recurrent urinary tract infections caused by susceptible strains of the organisms listed below.

Nebcin is usually active against most strains of the following organisms:

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  Proteus mirabilis, *Pr. morganii*, and *Pr. vulgaris*
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Klebsiella-Enterobacter-Serratia group
Citrobacter sp.
Providencia sp.
Staphylococci, including *Staphylococcus aureus* (coagulase-
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Nebcin has been studied in 3,506 patients. Close analysis of adverse reactions reported suggests that Nebcin provides a desirable balance of effectiveness and safety.

In the 3,506 case reports submitted to Eli Lilly and Company, drug-related side-effects (including abnormal laboratory values) were reported in 136 (3.9 percent) of the patients. Those of doubtful relationship to Nebcin were noted in 233 (6.6 percent). Adverse reactions were severe enough to warrant discontinuation of the drug in seventy cases.

WARNINGS

Patients treated with Nebcin should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.

Both vestibular and auditory ototoxicity can occur. Eighth-nerve impairment may develop if patients have preexisting renal damage and if Nebcin is administered for longer periods or in higher doses than those recommended.

Tobramycin is potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by cylindruria, oliguria, proteinuria, or evidence of nitrogen retention (increasing BUN, NPN, or creatinine). Evidence of impairment in renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.

Nebcin should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.

In the case of overdosage or toxic reactions, peritoneal dialysis or hemodialysis will help remove tobramycin from the blood.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 12 mcg./ml. should be avoided. Urine should be examined for increased excretion of protein, cells, and casts.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, and vancomycin, should be avoided.

Nebcin should not be given concurrently with potent diuretics. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Usage in Pregnancy – Safety of this product for use during pregnancy has not been established.

Bendush, C.L., and Weber, R.: Clinical Results with Tobramycin Sulfate: A Summary of Worldwide Experience, J. Infect. Dis. (Supplement) (in press).

Renal system: incidence of adverse effects

Adverse Reactions in the Renal System

Condition or Laboratory Value	Adverse Effects as Classified by Investigator	
	Related	Doubtful
Serum creatinine	36	29
BUN	21	43
Creatinine clearance	10	28
Casts	6	13
Blood urea	12	14
Albuminuria	1	4
Uric acid	1	0
WBC	1	5
RBC	0	5
	88 (in 53 patients)*	141 (in 105 patients)*

*Two patients are included in both categories; therefore, a total of 156 had 229 abnormal (related plus doubtful) adverse effects.

Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, have been reported with Nebcin, especially in patients on high dosage and/or prolonged therapy and particularly in those with known or suspected renal impairment. The accompanying table summarizes the renal effects found in the study group of 3,506 patients.

Nervous system: incidence of adverse effects

Adverse Reactions in the Nervous System

Condition	Number of Effects as Classified by Investigator	
	Related	Doubtful
Vestibular		
Dizziness	9	9
Vestibular disturbances	5	1
Nystagmus	2	0
Vertigo	2	0
Auditory		
Hearing decrease	5	1
Tinnitus	4	2
Temporary hearing loss	4	0
Headache	1	5
Taste	0	2
Apnea	0	1
Asthenia	0	1
Neuropathy (not specified)	0	1
	32 (in 23 patients)	23 (in 21 patients)

Adverse effects on both the vestibular and auditory branches of the eighth nerve can occur. Impairment of eighth-nerve function is most likely in patients with renal damage, especially in those on high dosage and/or prolonged therapy. Effects on vestibular and/or auditory function in the group of 3,506 patients are shown in the accompanying table.

In patients with normal renal function who do not receive Nebcin in higher doses or for longer periods of time than those recommended, the risk of toxic reactions is low. However, patients treated with Nebcin should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.

To maximize efficacy and minimize risk

1. Follow recommended dosage schedules for all patients; adjust dosage and/or dosage intervals in patients with impaired renal function.
2. Monitor patients whose renal function is initially normal but in whom oliguria or evidence of nitrogen retention (increasing serum creatinine, BUN, or NPN) develops during therapy.
3. Examine urine for an increase in protein, cells, and casts.
4. Monitor renal function in all high-risk patients—the elderly, debilitated, and those with impaired renal function caused by trauma, surgery, infection, or chemotherapy.
5. Monitor serum concentrations when feasible, and avoid prolonged levels above 12 mcg./ml. Determine serum concentrations if the dosage is increased above those usually recommended.
6. Assess auditory and vestibular function during prolonged treatment in patients with known or suspected renal impairment and in those with initially normal renal function who develop signs of renal dysfunction during therapy.
7. Avoid the concomitant or sequential use of drugs that are potentially ototoxic or nephrotoxic.

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WARNINGS

Patients treated with Nebcin should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.

Both vestibular and auditory ototoxicity can occur. Eighth-nerve impairment may develop if patients have preexisting renal damage and if Nebcin is administered for longer periods or in higher doses than those recommended.

Tobramycin is potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by cylindruria, oliguria, proteinuria, or evidence of nitrogen retention (increasing BUN, NPN, or creatinine). Evidence of impairment in renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.

Nebcin should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.

In the case of overdosage or toxic reactions, peritoneal dialysis or hemodialysis will help remove tobramycin from the blood.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 12 mcg./ml. should be avoided. Urine should be examined for increased excretion of protein, cells, and casts.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, and vancomycin, should be avoided.

Nebcin should not be given concurrently with potent diuretics. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Description: Tobramycin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from the actinomycete *Streptomyces tenebrarius*. Nebcin Injection is a clear and colorless sterile aqueous solution for parenteral administration. It is stable and requires no refrigeration.

Indications and Usage: Nebcin is indicated for the treatment of serious infections caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus* sp. (indole-positive and indole-negative), *Providencia*, *Klebsiella-Enterobacter-Serratia* group, *Citrobacter* sp., and staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).

Nebcin is indicated in the treatment of septicemia; central-nervous-system infections, including meningitis; neonatal sepsis; serious lower respiratory infections; gastrointestinal infections, including peritonitis; and serious skin, bone, and soft-tissue infections, including burns, caused by the susceptible organisms listed above. Clinical studies have shown Nebcin also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including Nebcin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity. Nebcin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Bacterial cultures should be obtained prior to and during treatment to isolate and identify etiologic organisms and to test their susceptibility to tobramycin. If susceptibility tests show that the causative organisms are resistant to tobramycin, other appropriate therapy should be instituted. In patients in whom gram-negative septicemia, neonatal sepsis, or meningitis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with Nebcin may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with Nebcin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the WARNINGS box above.

Contraindication: A history of hypersensitivity to tobramycin is a contraindication to its use.

Warnings: See WARNINGS box above.

Precautions: Specimens should be collected during therapy for examination, as recommended in the WARNINGS box.

Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of tobramycin (40 mg./Kg.). The possibility that prolonged or secondary apnea may occur should be considered if tobramycin is administered to anesthetized patients who are also receiving neuromuscular blocking agents, such as succinylcholine or tubocurarine.

Cross-allergenicity among aminoglycosides has been demonstrated.

If overgrowth of nonsusceptible organisms occurs, appropriate therapy should be initiated.

Adverse Reactions: *Nephrotoxicity*—Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, cylindruria, and increased proteinuria, have been reported, especially in patients with a history of renal impairment who are treated for longer periods or with higher doses than those recommended.

Neurotoxicity—Adverse effects on both the vestibular and auditory branches of the eighth nerve have been noted, especially in patients receiving high doses or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss.

NOTE: The risk of toxic reactions is low in patients with normal renal function who do not receive Nebcin in higher doses or for longer periods of time than those recommended.

Other reported adverse reactions possibly related to Nebcin include increased serum transaminase (SGOT, SGPT) and increased serum bilirubin; anemia, granulocytopenia, and thrombocytopenia; and fever, rash, itching, urticaria, nausea, vomiting, headache, and lethargy.

Suggested Dosage Guides—I.M./I.V.:

Usual dosage for adults, children, and older infants (normal renal function)—

3 mg./Kg./day administered in three equal doses every eight hours. In life-threatening situations, the dosage may be increased up to 5 mg./Kg./day administered in three or four equal doses. This dosage should be reduced to 3 mg./Kg./day as soon as clinically indicated. (Refer to Table 1 for dosage schedule.)

Dosage for neonates up to one week of age (normal renal function)—

Up to 4 mg./Kg./day may be given in two equal doses every twelve hours. The usual duration of treatment is seven to ten days.

Dosage guidelines for adult or pediatric patients with reduced renal function—

After a loading dose of 1 mg./Kg., subsequent dosage must be adjusted either with reduced doses at eight-hour intervals or with normal doses at prolonged intervals. To determine the reduced dose at eight-hour intervals, see the convenient nomogram in the package literature.* To calculate normal dosage at prolonged intervals (if the creatinine clearance rate is not available and the patient's condition is stable), the following formula may be used:

1 mg./Kg. q. (6 × serum creatinine) h.

Neither regimen should be used when dialysis is being performed.

I.V. Administration—The usual volume of diluent for adults is 50 to 100 ml. For children, the volume of diluent should be proportionately less than for adults. The diluted solution usually should be infused over a period of twenty to sixty minutes.

Table 1. Dosage Schedule Guide for Adults with Normal Renal Function (Dosage at Eight-Hour Intervals)

For Patient Weighing Kg.	Lb.	Usual Dose for Serious Infections 1 mg./Kg. q. 8 h. (Total, 3 mg./Kg./day)		Maximum Dose for Life-Threatening Infections **(Reduce as soon as possible)** 1.66 mg./Kg. q. 8 h. (Total, 5 mg./Kg./day)	
		mg./dose q. 8 h.	**ml./dose†**	**mg./dose q. 8 h.**	**ml./dose†**
120	264	120 mg.	3 ml.	200 mg.	5 ml.
115	253	115 mg.	2.9 ml.	191 mg.	4.75 ml.
110	242	110 mg.	2.75 ml.	183 mg.	4.5 ml.
105	231	105 mg.	2.6 ml.	175 mg.	4.4 ml.
100	220	100 mg.	2.5 ml.	166 mg.	4.2 ml.
95	209	95 mg.	2.4 ml.	158 mg.	4 ml.
90	198	90 mg.	2.25 ml.	150 mg.	3.75 ml.
85	187	85 mg.	2.1 ml.	141 mg.	3.5 ml.
80	176	80 mg.	2 ml.	133 mg.	3.3 ml.
75	165	75 mg.	1.9 ml.	125 mg.	3.1 ml.
70	154	70 mg.	1.75 ml.	116 mg.	2.9 ml.
65	143	65 mg.	1.6 ml.	108 mg.	2.7 ml.
60	132	60 mg.	1.5 ml.	100 mg.	2.5 ml.
55	121	55 mg.	1.4 ml.	91 mg.	2.25 ml.
50	110	50 mg.	1.25 ml.	83 mg.	2.1 ml.
45	99	45 mg.	1.1 ml.	75 mg.	1.9 ml.
40	88	40 mg.	1 ml.	66 mg.	1.6 ml.

†Applicable to all product forms except Nebcin, Pediatric, Injection (see How Supplied).

How Supplied: Ampoules Nebcin® (tobramycin sulfate, Lilly) Injection, 80 mg. (equivalent to tobramycin) per 2 ml., 2 ml., rubber-stoppered.

Ampoules Nebcin, Pediatric, Injection, 20 mg. (equivalent to tobramycin) per 2 ml., 2 ml., rubber-stoppered.

Hyporets® (disposable syringes, Lilly) Nebcin Injection, 60 mg. (equivalent to tobramycin) per 1.5 ml., 1.5 ml., and 80 mg. (equivalent to tobramycin) per 2 ml., 2 ml., in packages of 24.

Each ml. also contains 5 mg. phenol as a preservative, 3.2 mg. sodium bisulfite, 0.1 mg. disodium edetate, and water for injection, q.s. Sulfuric acid and/or sodium hydroxide may have been added to adjust the pH. [030476]

Lilly

Additional information available to the profession on request.

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Indianapolis, Indiana 46206

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*An alternate rough guide for determining reduced dosage at eight-hour intervals (for patients whose steady-state serum creatinine values are known) is to divide the normally recommended dose by the patient's serum creatinine.

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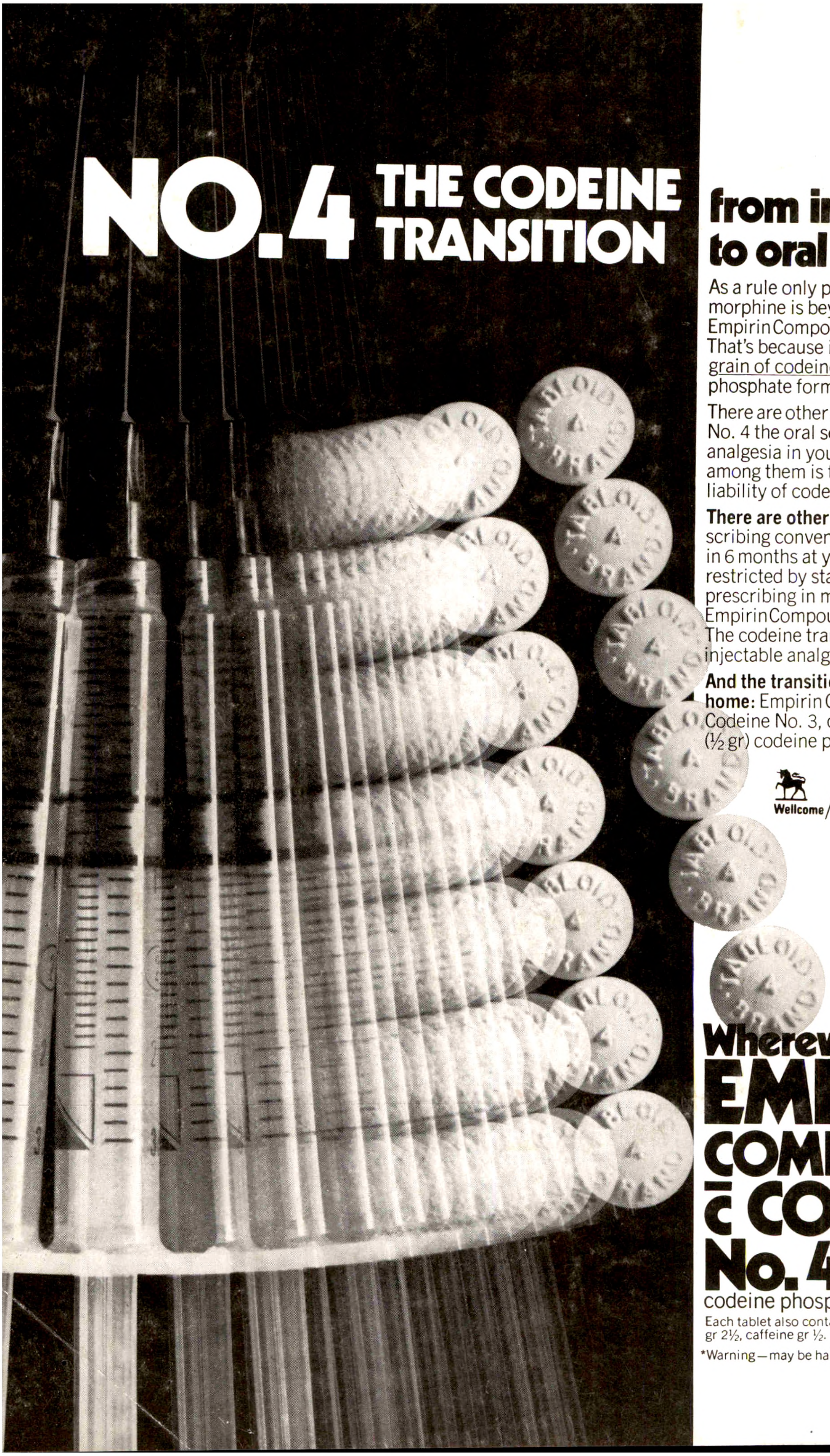

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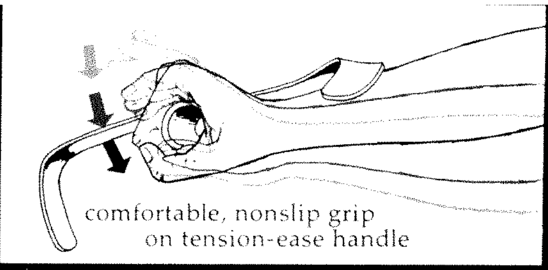
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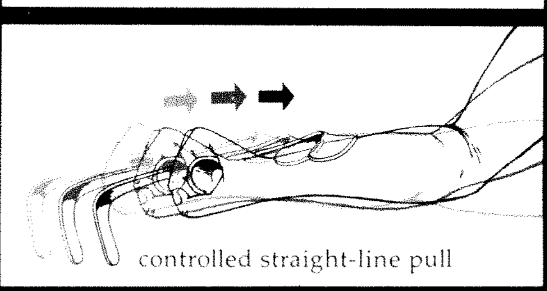
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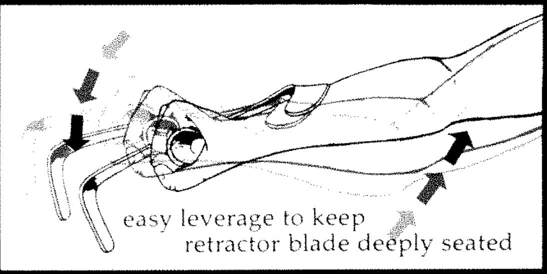
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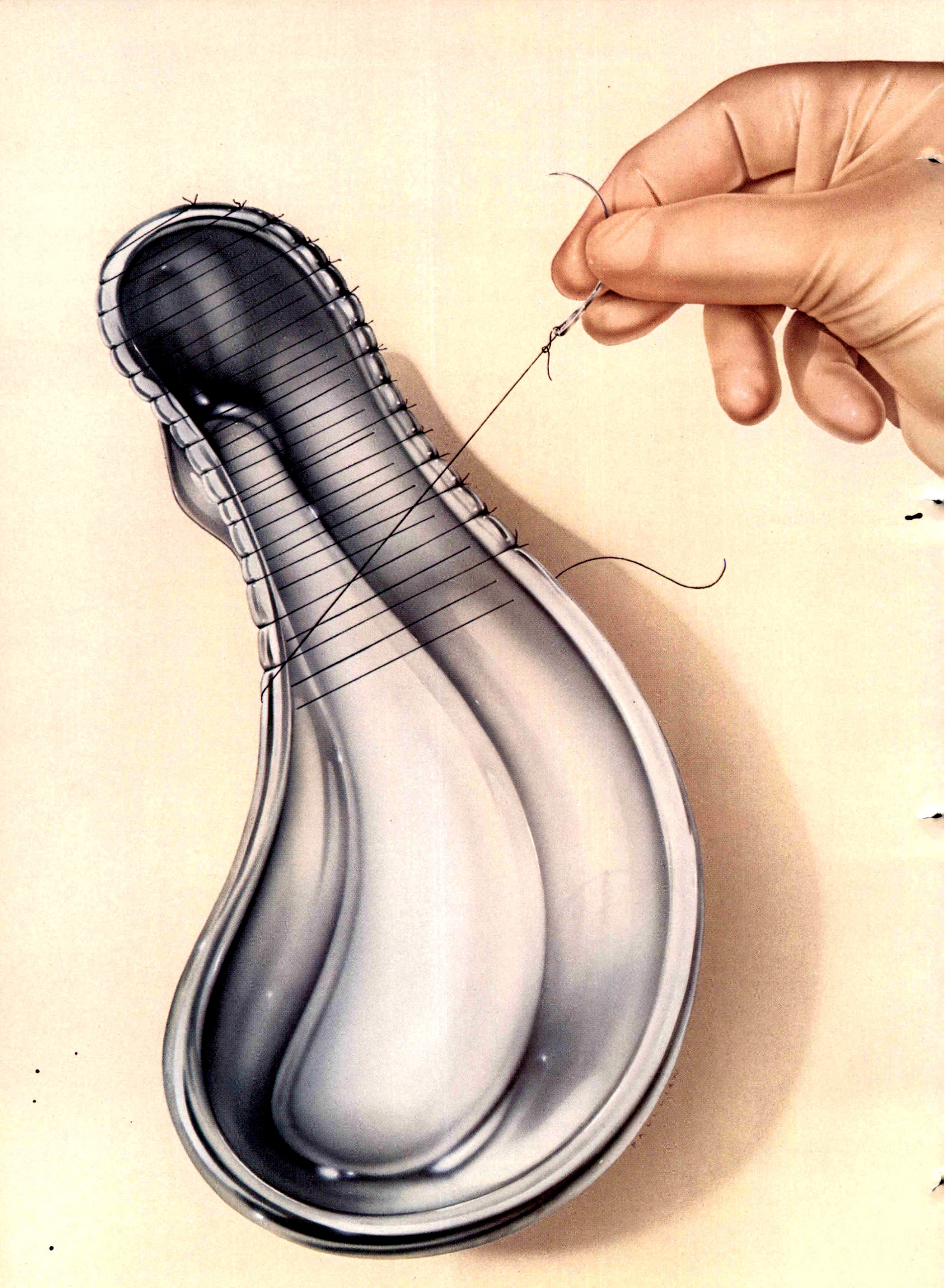

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BRIEF SUMMARY OF PRESCRIBING INFORMATION
EMETE-CON® (benzquinamide HCl) IM/IV

CONTRAINDICATIONS. Contraindicated in individuals who have demonstrated hypersensitivity to the drug.

WARNINGS. *Use in Pregnancy.* No teratogenic effects of benzquinamide were demonstrated in reproduction studies in chick embryos, mice, rats and rabbits. The relevance of these data to the human is not known. However, safe use of this drug in pregnancy has not been established and its use in pregnancy is not recommended.

Use in Children. As the data available at present are insufficient to establish proper dosage in children, use in children is not recommended.

Intravenous use. Sudden increase in blood pressure and transient arrhythmias (premature ventricular and auricular contractions) have been reported following intravenous administration of benzquinamide. Until a more predictable pattern of the effect of intravenous benzquinamide has been established, the intramuscular route of administration is considered preferable. The intravenous route should be restricted to patients without cardiovascular disease and receiving no pre-anesthetic and/or concomitant cardiovascular drugs.

PRECAUTIONS. Benzquinamide, like other antiemetics, may mask signs of overdosage of toxic drugs or may obscure diagnosis of such conditions as intestinal obstruction and brain tumor.

ADVERSE REACTIONS. Drowsiness appears to be the most common reaction. One case of pronounced allergic reaction has been encountered, characterized by pyrexia and urticaria.

System Affected

Autonomic Nervous System: Dry mouth, shivering, sweating, hiccoughs, flushing, salivation, blurred vision.

Cardiovascular System: Hypertension, hypotension, dizziness, atrial fibrillation, premature auricular and ventricular contractions.

Central Nervous System: Drowsiness, insomnia, restlessness, headache, excitement, nervousness.

Gastrointestinal System: Anorexia, nausea.

Musculoskeletal System: Twitching, shaking/tremors, weakness.

Skin: Hives/rash.

Other Systems: Fatigue, chills, increased temperature.

OVERDOSAGE. *Manifestations:* On the basis of acute animal toxicology studies, gross Emete-con overdosage in humans might be expected to manifest itself as a combination of Central Nervous System stimulant and depressant effects. This speculation is derived from experimental studies in which intravenous doses of benzquinamide, at least 150 times the human therapeutic dose, were administered to dogs.

Treatment: There is no specific antidote for Emete-con overdosage. General supportive measures should be instituted, as indicated. Atropine may be helpful. Although there has been no direct experience with dialysis, it is not likely to be of value, since benzquinamide is extensively bound to plasma protein.

CAUTION. Federal law prohibits dispensing without prescription.

More detailed professional information available on request.

REFERENCES:

1. Zauder, H. L., et al.: Prophylaxis of postoperative emesis. Scientific Exhibit presented at 122nd Annual Convention of the American Medical Association, New York, June 23-27, 1973.
2. Lutz, H., and Immich, H.: Curr. Ther. Res. *14*:178, April, 1975.
3. Steen, S. N., and Yates, M.: Anesthesiology *36*:519, May, 1972.

*Please see brief summary for contraindications and other reported adverse reactions.

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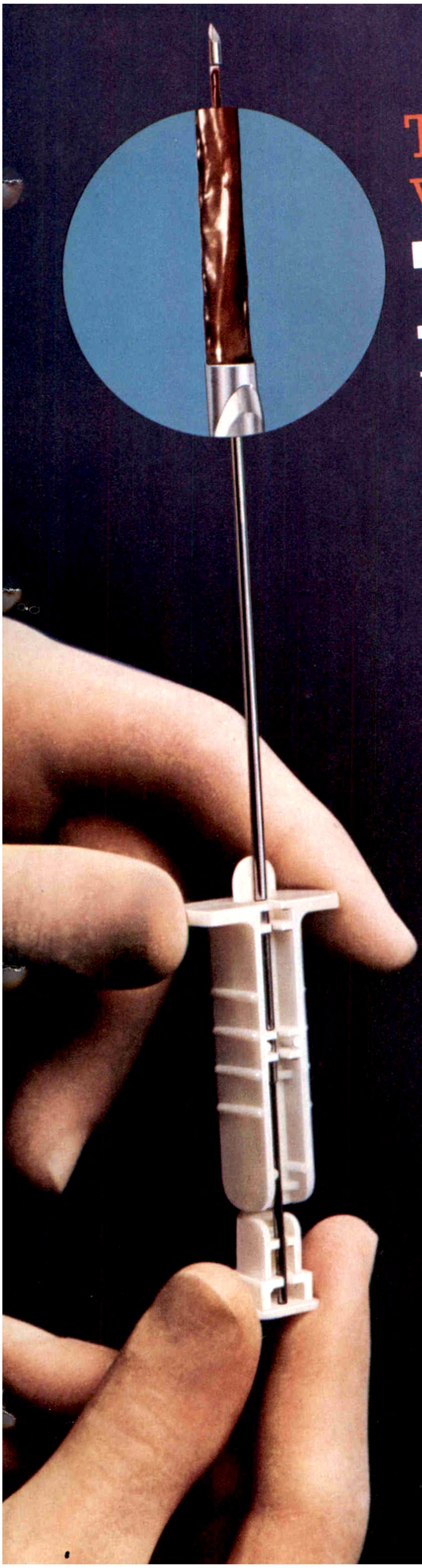

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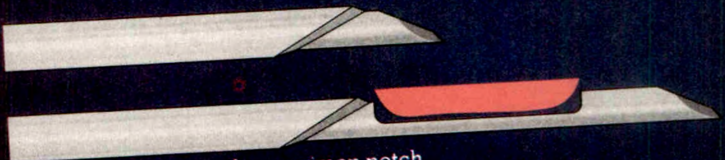
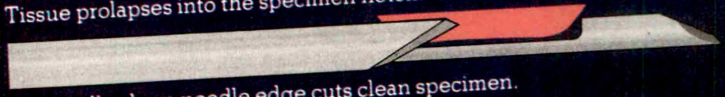
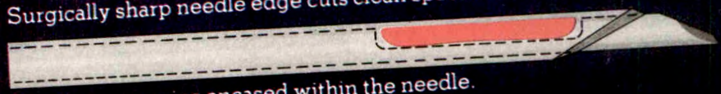


Tissue prolapses into the specimen notch.



Surgically sharp needle edge cuts clean specimen.



Specimen remains encased within the needle.

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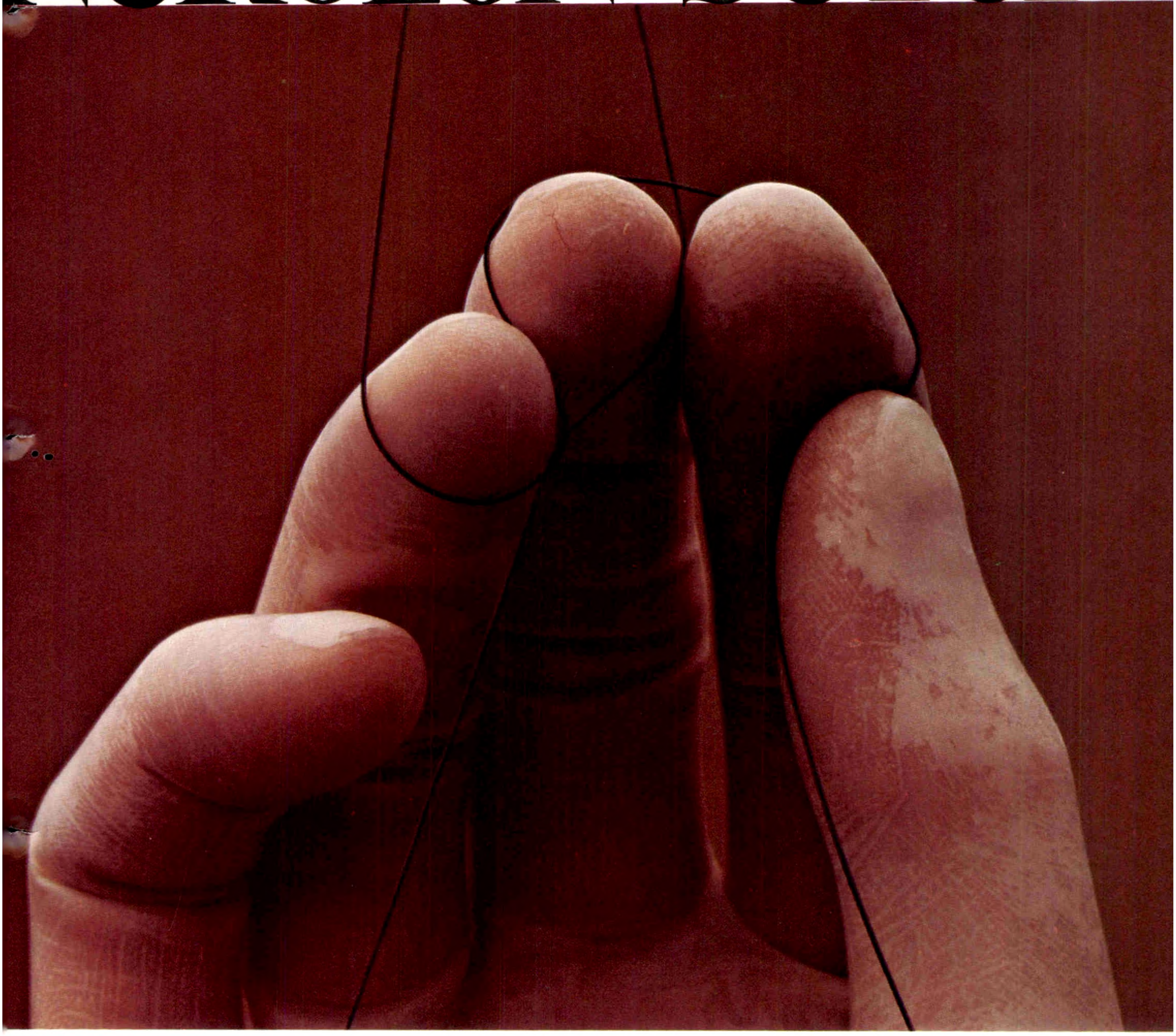

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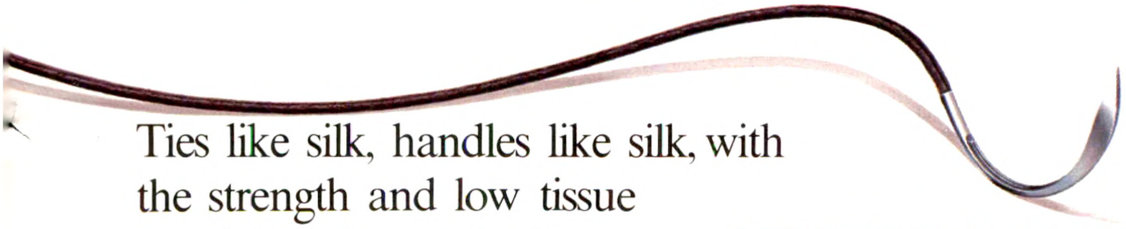

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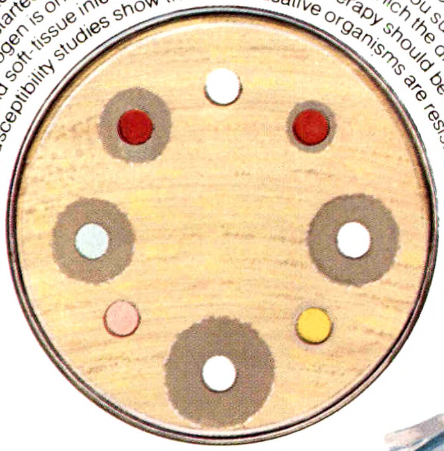
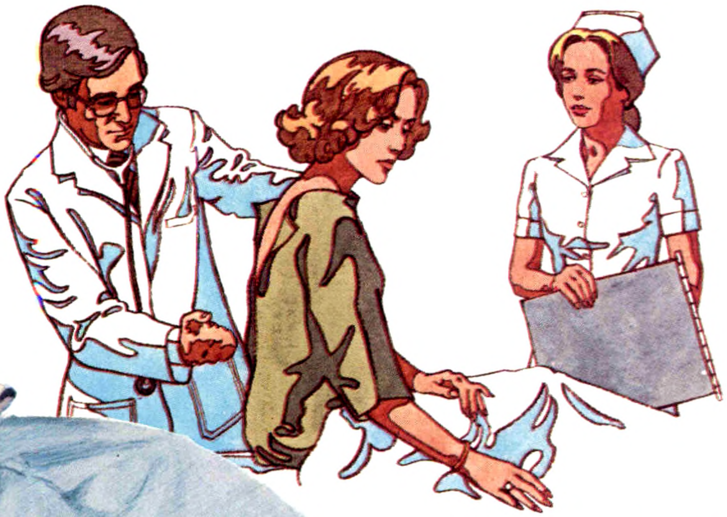
Appropriate cultures should be taken, but Keflin® (cephalothin sodium, Lilly) may be started before susceptibility results are obtained if you suspect the causative pathogen is one of the susceptible organisms for which the drug is indicated in skin and soft-tissue infections.* Other antibiotic therapy should be instituted if susceptibility studies show that the causative organisms are resistant.

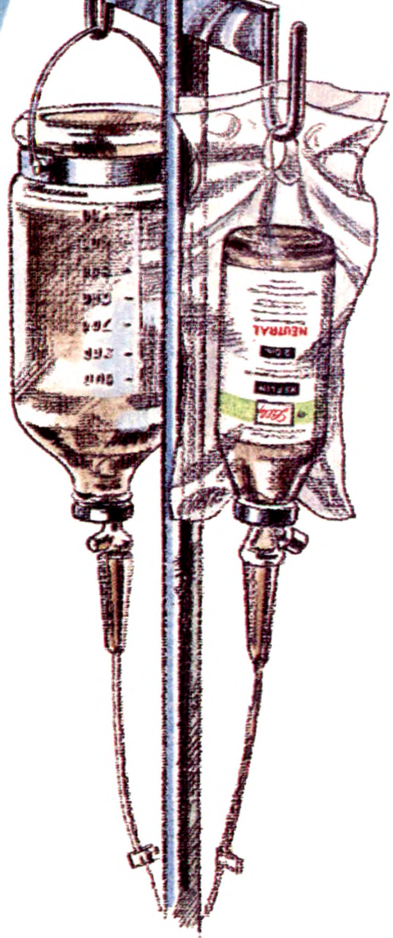


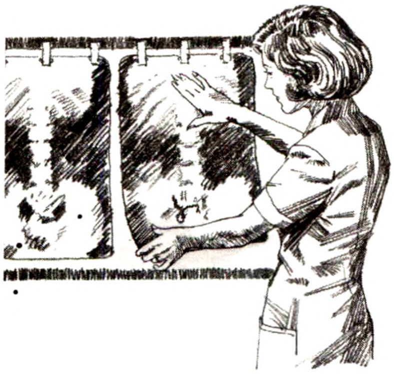


In the immunosuppressed patient, usual clinical signs and symptoms of infection may be missing or not clear. Hence, diagnosis and initiation of proper therapy become most urgent.

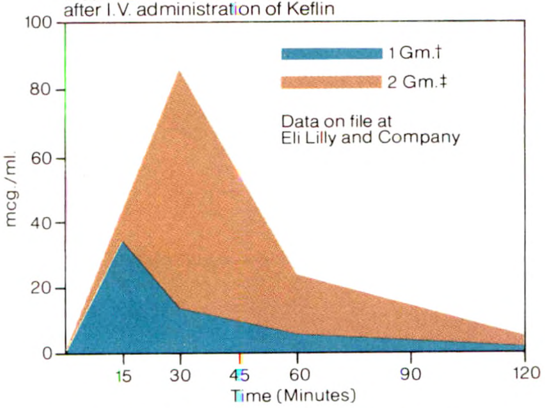
An initial loading dose of 1 to 2 Gm. of Keflin may be given regardless of the patient's renal status. Patients with impaired renal function should be placed on a reduced dosage schedule. Usual doses in such individuals may result in excessive serum concentrations.

Keflin may be administered I.V. or I.P. in dosages as high as 12 Gm. per day (in life-threatening infections).





Mean serum concentrations after I.V. administration of Keflin



†Administered to six patients by rapid I.V. infusion.
‡Administered to ten patients over a thirty-minute period.

*Skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*.

Please see opposite page for summary of prescribing information.

In serious skin and soft-tissue infections*

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Keflin should be given cautiously to penicillin-sensitive patients.

It is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

* Skin and soft-tissue infections, including peritonitis, caused by susceptible strains of staphylococci (both penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Esch. coli, Pr. mirabilis,* and *Klebsiella.*

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†Equivalent to cephalothin

Brief Summary.
Consult the package literature for prescribing information.

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Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli, Proteus mirabilis,* and *Klebsiella*

Bone and joint infections caused by staphylococci (penicillinase and nonpenicillinase-producing)

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy—Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side-effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: Maculopapular rash, urticaria, pain, induration, tenderness, elevation of temperature, reactions resembling serum sickness, anaphylaxis, eosinophilia, drug fever, neutropenia, thrombocytopenia, hemolytic anemia, thrombophlebitis, transient rise in SGOT and alkaline phosphatase, rise in BUN, decreased creatinine clearance, and a positive direct Coombs test have been reported. [111475S]

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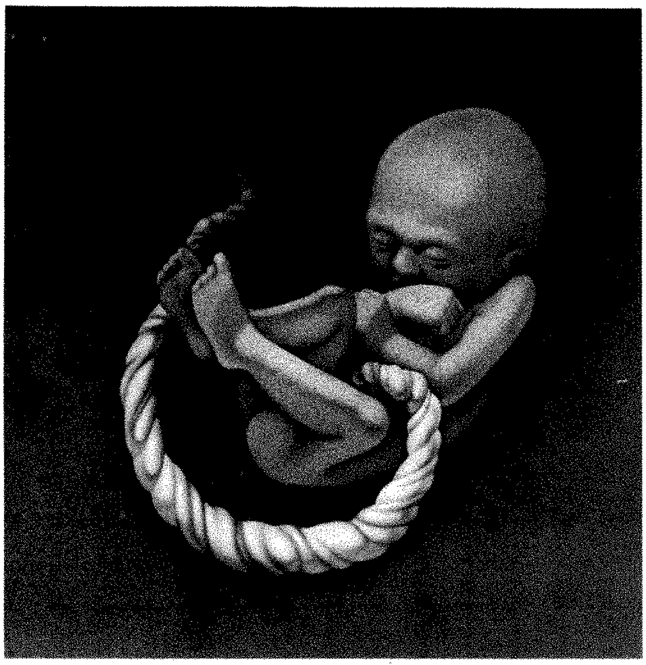

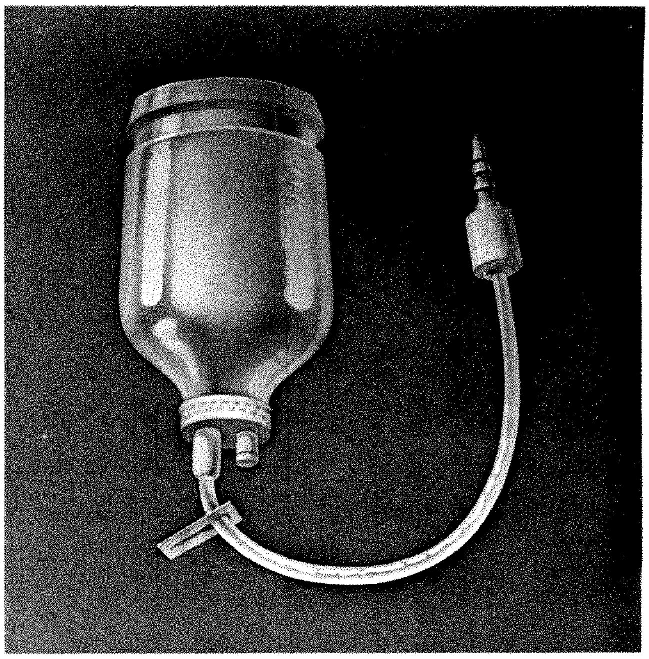

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BRIEF SUMMARY

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ANNALS OF SURGERY

Vol. 183 June 1976 No. 6

Vagotomy and Drainage Procedure for Duodenal Ulcer:

The Results of Seventeen Years' Experience

J. PATRICK O'LEARY, M.D., E. R. WOODWARD, M.D., J. I. HOLLENBECK, M.D., L. R. DRAGSTEDT, PH.D., M.D.*

From the Department of Surgery, College of Medicine,
University of Florida, Gainesville,
Florida, 32610

During the 10 years prior to January, 1968, 455 duodenal ulcer patients were operated upon at the University of Florida affiliated hospitals. The early results were reported in 1969. The present study is a followup of the same patients now 7 to 17 years after vagotomy and drainage. Twenty-four per cent were lost to followup. The ulcer recurrence rate was 5.8 per cent. All the recurrent ulcers that were not gastric in location (4.9%) occurred within 5 years after the original operative procedure with a mean of 2.6 years. The gastric ulcers (0.9%) occurred at a much later date with a mean of 6 years. It is concluded that vagotomy and gastric drainage is a satisfactory modality of therapy for duodenal ulcer. It can be accomplished with an acceptable morbidity and mortality and the long-term recurrence rate is low. If recurrences due to incomplete vagotomy do not occur within 5 years, they are unlikely to recur.

THE RESULTS of the accepted modalities of surgical therapy for duodenal ulcer have been generally good. Only small differences exist between the various procedures; however, because of the large number of patients treated each year these differences become significant. Many authors have alluded to the higher incidence of recurrence after vagotomy and a drainage procedure as being its major drawback.[1,4,7] This paper deals with the results of vagotomy and drainage procedure on 455 patients who have now been followed from 7 to 17 years.

Clinical Material

The patients who comprise the population for this study were operated upon between October of 1958 and January of 1968. These patients were first reported in the *Annals of Surgery* in 1969.[3] Followup has now been extended to a minimum of 7 years and a maximum of 17 years. In the original study there were 455 patients, seven of whom were lost to followup. In the present study 348 patients were evaluated. Of these, 85 are now dead. Only one of the deaths was related to the patient's ulcer disease and occurred at the time of a subsequent gastric resection. One hundred and seven of the 455 were lost to followup leaving 76% of the original patients accounted for in the study. The demographic data for this group were reported in the previous evaluation. Significant parameters reveal that there was a preponderance of Caucasian versus Negro patients (382/72), males versus females (415/40), skilled and unskilled versus professional and executive individuals (280/67). The age range in the group was from 8 years to 83 years with an average age of 49 years; 45% were 50 years old or older. The population of the present group reflects the increasing age

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Presented at the Annual Meeting of the Southern Surgical Association, December 8–10, 1975, The Homestead, Hot Springs, Virginia.

This work has been supported by National Institutes of Health grant number AM-04178.

Reprint requests: J. P. O'Leary, M.D., Department of Surgery, Box J-286, College of Medicine, University of Florida, Gainesville, Florida 32610.

* Deceased.

TABLE 1. *Indication for Operation*

	No. Patients	Per cent
Elective 401/455 (88%)Patients		
1. Intractability	265/401	66
2. Inability to adhere to medical treatment	22/401	5
3. Recurrent hemorrhage previous perforation symptoms of hiatus hernia	68/401	17
4. Obstruction	46/401	12
Emergency 54/455 (12%)Patients		
1. Hemorrhage	46/54	85
2. Perforation	8/54	15

of the group as a whole, but was consistent with the age range distribution of the original group.

Two hundred and seventy-three (60%) had suffered at least one hemorrhage prior to their surgery and 79 (17%) had a history of previous perforation. Forty-five patients were operated upon as emergencies and 409 (90%) had undergone medical management. Forty per cent of all the patients had coexistent diseases at the time of surgery.

The indications for surgery are listed in Table 1. The great majority were done for intractability (66%). The operative mortality was 1% in 401 elective procedures and 2% in 44 emergency procedures.

In 416 (91%) a vagotomy and pyloroplasty was the procedure of choice while in 39 (9%) the drainage procedure was a gastroenterostomy. A tube gastrostomy was employed in 94% of the cases (Table 2).

Followup

Followup was accomplished by direct evaluation in the clinic, home visits, written responses to questionnaires or telephone conversations. In instances where questions arose, the patient's family physician was contacted directly. All patients in this series were followed a minimum of 7 years and some as long as 17 years postoperatively. The average followup was 10 years.

Recurrences

A standard definition of recurrent ulcer disease was used as described by Weinberg[11] i.e.: 1) persistence of ulceration following operation; 2) ulceration in a new site; 3) recurrence after an interval of apparent complete healing; 4) any suspected recurrence of ulceration unless proven not to exist. These are the same criteria used in the earlier study.

In the 257 patients who were evaluated, 6 had developed recurrent duodenal or marginal ulcer and 4 had developed a gastric ulcer. In the group studied, this is an incidence of recurrence of 10 out of 257 or 4%. When the 10 recurrences in this group are added to the 16 recurrences found in the original study, the overall incidence of recurrence is 5.8% (Table 3).

Of the 6 patients who developed a duodenal recurrence, 4 had had a vagotomy and pyloroplasty with gastrostomy while two had had a vagotomy and gastroenterostomy. The latent period from the time of surgery to recurrence ranged from one year to 5 years with a mean of 2.6 years. Five of these patients required reoperation. One of the patients with a gastroenterostomy bled 1½ years after his original operation. He was demonstrated to have another duodenal ulcer; his small gastroenterostomy was taken down and a Finney pyloroplasty fashioned. The other patient with a gastroenterostomy developed a marginal ulcer two years after his original surgery. He was operated upon and an antrectomy with gastroduodenostomy was performed. Both patients are now free of disease.

Three of the remaining four patients with recurrent duodenal ulcers have undergone gastric resection. One of these had recurrent hemorrhage while the others had recurrent symptoms. The fourth patient has bled, but has not required surgical intervention. All of these patients had experienced recurrent abdominal pain.

In the group of 4 patients who developed a gastric ulcer, one had a vagotomy with gastroenterostomy while the remaining three had a vagotomy and pyloroplasty. The latent period varied from 5 to 8 years with a mean of 6 years. Two of the ulcers were discovered at autopsy. One was described as an acute gastric erosion and occurred in a patient who survived two days after a myocardial infarction. The second was a chronic ulcer found in an elderly man who died of pneumonia. The third was treated with a gastric resection and gastroduodenostomy while the fourth was treated nonoperatively. In this group, two had originally been

TABLE 2. *Operative Procedure*

	No. Patients	Per cent
Primary		
Vagotomy and pyloroplasty	416/455	91
1. Weinberg	407/416	
2. Finney	9/416	
Vagotomy and Gastroenterostomy	39	9
Total	455	100
Gastrostomy	428	94
Incidental (120 or 26% patients)		
Hiatal herniorrhaphy	48	11
Cholecystectomy	21	5
Appendectomy	16	3
Splenectomy	6	1
Other	29	6

TABLE 3. *Recurrent Ulcer*

	No. Patients/Average Followup		
Overall	3¼ Years	10 Years	Per cent
Proved	13/443	23/443	5.2
Suspected	3/443	3/443	.6
TOTAL	16/443	26/443	5.8

TABLE 4. *Results*

Highly pleased	57%
Satisfied	30%
Not satisfied	7%
Highly dissatisfied	6%
Feel better	87%
Feel same	7%
Feel worse	6%

operated upon for intractability, one for pain associated with hemorrhage, and one because of repeated bouts of obstruction. Two of the individuals in this group had had previous gastric procedures.

Dumping

Although there was a significant incidence of patients complaining of abdominal distress, true "dumping" was relatively infrequent. The dumping syndrome was divided into two major classifications. The first group included those who demonstrated the effects of volume shifts after the ingestion of a food; this was termed early dumping. The second group included those who developed symptoms of hypoglycemia two to 4 hours after eating; this was termed late dumping.

Eight patients demonstrated early dumping while two exhibited late dumping. One patient demonstrated some symptoms of both. The majority of patients controlled their symptoms by regulation of their diet. None has required surgical intervention to alleviate these symptoms.

Diarrhea

Diarrhea was present in 16% of the series. The bulk of the patients who responded felt that it was mild, but 5% felt that it was a rather severe problem. Two of the patients had their lives moderated by the presence of this annoying symptom. It was interesting to note that three patients stated the ingestion of antacids diminished the frequency of their diarrhea. Others complained of frequent stools, but true diarrhea was not present.

Subjective Evaluation

Patients were asked to answer a standard questionnaire in regard to a variety of different symptoms that could be associated with their operations. Eighty-seven per cent of patients were either highly pleased or satisfied with the results of their surgery while 7% were not satisfied and 5% were highly dissatisfied (Table 4). Despite this apparent generally positive feeling toward the procedure, 53% of patients complained that they were still having some stomach problems (Table 5). Pain of varying degrees was a problem in 40% of patients. Of the 37 patients who were able to compare it to their preoperative pain, 62% felt that it was the same while 8% felt that it was less severe and 30% felt that it was more severe.

Vomiting was not a problem in 86% of the patients. Of the 14% in whom it was a problem, 3% felt the problem was mild, 4% felt the problem was moderate, and 7% felt that the problem was severe. Bloating was present in 55% of the patients. It was classified as mild in 14%, moderate in 24% and severe in 17%.

Forty-two or 16% of the patients had experienced bleeding from the G.I. tract. Seven of these 42 patients had apparently rebled from ulcer disease and were listed as recurrences. The rest of the patients bled from other parts of the G.I. tract. The most common site of origin was hemorrhoids. All patients who responded positively to this item were contacted directly or evaluated by their family physician.

The majority of the patients, 82%, stated that they felt better while 12% felt that they were the same and 6% felt that they were worse. Six of this latter group of 15 exhibited a form of the dumping syndrome.

Discussion

Morbidity and mortality from vagotomy and pyloroplasty and vagotomy with limited gastric resection have been extensively reported.[1,3,4,7–10] In the well-trained hands of the investigators reporting these series the differences in mortality are small, but probably real. In many series mortality after a gastric resection, regardless how small, is 1½ to 3 times that after a vagotomy and pyloroplasty.[6,9,10] These data are gathered from centers where there is great interest in the care and treatment of duodenal ulcer. Although in some of these centers

TABLE 5. *Subjective Evaluations*

Symptoms	None	Mild	Moderate	Severe
Pain	60%	7%	21%	12%
Vomiting	86%	3%	4%	7%
Diarrhea	84%	8%	3%	5%
Bloating	45%	14%	24%	17%
Stomach Problems		Yes 53%	No 47%	

much of the surgery is done by housestaff, the procedures are carefully supervised and experienced surgical judgment is exercised. When a difficult duodenum is encountered, the experienced gastrointestinal surgeon assesses the situation and chooses an alternative to gastric resection. Certainly not all duodenums lend themselves to gastric resection, regardless of how small the resection may be. The potential problem resides at the line of the anastomosis or closure, not during the actual resection. The reason that the skilled surgeon's mortality with gastric resection approaches that of a vagotomy and drainage procedure is that he avoids potentially lethal problems by selecting out the high risk patient in the operating room. The surgeon who infrequently faces these problems may not be as adept in making these decisions.

Morbidity is lower after a vagotomy and drainage procedure than after a vagotomy and limited gastric resection. Suture line disruption is less likely after a pyloroplasty than after an antrectomy. Likewise, pancreatic injury and subhepatic abscess are less likely after the former than after the latter. If the reconstruction after a gastrectomy is a gastrojejunostomy, then the patient is at risk for various postgastrectomy syndromes which are associated with the jejunal and duodenal limbs.[5] These are obviated by a vagotomy and pyloroplasty. Bile gastritis has been reported after a vagotomy and pyloroplasty, but it is certainly more common after a gastrectomy, especially if a Billroth II gastrojejunostomy has been constructed.[2]

In this series approximately 95% of the procedures in the Veterans Administration Hospital and approximately 75% of the procedures in the University Hospital were performed by resident surgeons. Yet the mortality and morbidity were acceptably low. We feel that the procedure is relatively simple and can be learned quickly.

As alluded to earlier, although there is only a small difference in the mortality, it is still significantly higher after a gastrectomy than after a vagotomy and drainage procedure. Although this difference is small, because of the large number of individuals operated upon each year the number of lives lost is significant. If a recurrence develops, the patient can be reoperated upon and a resection performed with no greater risk than other surgeons would accept for the primary procedure. The final question then seems to be the difference in the incidence of recurrence in patients after these procedures. It has been postulated that as large series of patients who have had vagotomy and a drainage procedure are followed for protracted periods of time, the incidence of recurrence will steadily increase. This has not been the finding in this study.

The recurrence rate of peptic ulcer disease after a vagotomy and drainage procedure is 5.8%. Although the followup is only 76%, comparisons between the Negro/Caucasion distribution ratio and the shape of the age distribution curve between the present patient population and the original series suggests that a representative sample has been obtained.

All of the recurrences of duodenal ulcer occurred within the first 5 years after surgery with an average lapse time of 2.6 years. When a patient developed a gastric recurrence, it appeared between 5 and 8 years postoperatively with an average lapse time of 6 years.

All of the patients who developed recurrences that were not gastric ulcers developed them less than 5 years after their operation. Since all of the patients have now been followed between 7 and 17 years with the majority being followed more than 10 years, we believe that the vast majority of recurrences after incomplete vagotomy and pyloroplasty will occur within the first 5 years. Late recurrences in the form of gastric ulcer are less common and have a latent period over 5 years. It has been our experience that these are often associated with unrelated acute illnesses or chronic debilitating diseases.

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Discussion

Dr. J. Lynwood Herrington, Jr. (Nashville): I believe that this recurrent ulcer rate, after truncal vagotomy and pyloroplasty, of 6%, and Jack Ferris' recurrence rate of 3.5%, are perhaps the best reported in this country. However, I think that we should keep in mind that in Dr. Woodward's series, 24% of his patients were lost to followup.

Unfortunately, not all surgeons have experienced such a low recurrence rate as Dr. Woodward has just described. The average recurrence rate throughout this country varies from his low rate up to about 15%, with an average recurrence rate of about 10% or above. We have had the sad experience of noting a recurrent ulcer rate of 18% following truncal vagotomy and pyloroplasty in just under 200 patients. Most of these cases were operated upon back in the late 1960's.

Dr. Sawyers and Dr. Scott currently in a series of 85 patients, using gastric selective vagotomy—not parietal cell vagotomy, but gastric selective vagotomy—with pyloroplasty have noted an acceptable recurrence rate of just under 3%. The longest followup is between five and six years.

However, as many of you know, Eric Amdrup and his group at Copenhagen, using gastric selective vagotomy and pyloroplasty, have had a recurrence rate of around 8%.

With gastric selective vagotomy, there is a lower incidence of positive Hollander tests, as compared to the truncal technique. Some currently speculate that this is due to the intact celiac and the hepatic rami exerting an inhibitory effect on the gastric antrum, perhaps through the liberation of the VIP and the GIP hormones, and is not related to the fact that a better technical job is performed using the gastric selective technique.

Now, the work with truncal vagotomy and antrectomy, begun in Nashville by the late Dr. Leonard Edwards early in 1947, has continued to date. Our group at Vanderbilt Hospital and the St. Thomas Hospital have now performed the procedure in just under 3800 patients during the last 29 years. Our overall mortality has been 2%, and the mortality in elective operations has been 1%. The operative mortality for the massively bleeding patient over age 60 has been 6.3%. The ulcer recurrence has been 0.6%, with each of the recurrences occurring within a 24 month period following the operation. We have not noted recurrences during the long-range followup.

Of course, many of our patients during the past 29 years have died during the followup study, but 2000 patients have now been followed in excess of ten years. I think these results are almost identical to those reported by George Jordan and Louis Palumbo. And we certainly share the view, strongly elucidated by Paul Jordan when he stated that except in the high risk patient—and if you eliminate the higher risk patient—that the mortality accompaning vagotomy-pyloroplasty and truncal vagotomy-antrectomy is just about the same.

At present we continue to apply truncal vagotomy-antrectomy to the vast majority of our ulcer patients, and even those with complete pyloric obstruction or in the massively bleeding ulcer patient who has a large, deep, penetrating ulcer. We frequently leave the deep, penetrating ulcer intact on the pancreas, and do a Billroth I reconstruction, which is our preference. We have noted about an equal degree of recurrence among the Billroth I and Billroth II reconstructions, even though serum gastrin levels are elevated after the B.I, as just mentioned by Jim Thompson. I personally do only about one truncal vagotomy with pyloroplasty each year.

(Slide) This shows our method of reconstruction, using the Billroth I technique. Even with the vast majority of deep, posterior, penetrating ulcers, we leave the ulcer attached to the pancreas, and just bring the mucosa of the greater curve of the stomach pouch over the ulcer, and leave the ulcer exteriorized, so to speak. I think, certainly in my experience, that this is associated with less morbidity and less mortality than closing the duodenal stump or mobilizing it farther and doing a Nissen closure or a Strauss maneuver.

Dr. Ward O. Griffen, Jr. (Lexington, Kentucky): I hesitate to rise. I would like to congratulate Dr. Woodward on a fine followup of the 455 patients. My hesitancy comes from the fact that our institution and I have reported the highest recurrence rate following vagotomy and pyloroplasty in the literature.

In 1965, when we reported on 112 patients, we had 21 patients who had recurrent ulcer, for a 19% incidence. That figure has now risen to 28 patients out of the original 112, for a recurrence rate of exactly 25%.

I hasten to mention, though, that in the original group of 112 patients, only 11% were operated on for intractability as the only indication for their operation. The series reported tonight had intractability as the indication for operation in some 71.6%, if you count the 6% who failed to adhere to a medical regimen.

I would like to ask Dr. Woodward to identify for me the factors that go into intractability, because it may be that the patient with only intractability as the complication of his duodenal ulcer may have less severe disease which is now amenable to the simpler operations.

I believe, too, that he has answered one of the questions that has always plagued me—why his recurrence rate is so low—and that was when he rather quickly passed over the fact that in a patient who has had severe bleeding but who has stopped bleeding, he apparently performs vagotomy and antrectomy as an elective procedure, rather than doing vagotomy and pyloroplasty. I suspect that means that he is selecting out the more severe ulcer diathesis for the bigger operation.

I too am intrigued by the 24% lost to followup rate. If half of those patients had recurrent ulcer, then their recurrence rate might approximate ours.

Dr. George L. Ivrin, III (Miami, Florida): (Slide) Dr. Woodward mentioned the difference in our operative mortality, and said that most patients who come in bleeding in Gainesville are admitted on the surgical service, and operated on right away.

That's well and good, but there are a number of other differences in these published series to which I'd like to call your attention. This slide shows his 1968 data with a very low operative mortality. Ours is 10%. By the way, this column shows Dr. Herrington's results. We missed the last 300 patients reported today, but these 3,584 patients made up his last report! These are Dr. Palumbo's recently reported patients, and the figures in this column were reported by Dr. Wolf in Richmond.

I'd like to call your attention to the fact that the mean ages of the groups are different, ours being the highest. Patients over 50 years of age are quite different in all of these reports. Sixty three per cent of our patients in South Florida are over 50 years of age. Intractability as the indication for operation is pretty high in everybody's group except ours. We get these patients very late.

If you will look at the number of elective operations: only two thirds of our compared to 88% to 90% in the other series were done electively. I think you will find that everyone's elective operative mortality is pretty good, with our being equal to theirs. Emergency operations: 10%, 9%, 12%—were compared to 36% of our patients who were done under emergency conditions.

One of the ways that we can explain the difference in operative mortality is by looking at the per cent of each entire series operated on as an emergency for hemorrhage: 3% in Dr. Herrington's, 6% in Richmond, 8% in Dr. Palumbo's, 10% in Dr. Woodward's, and 19% in the Miami series. Only the Miami group had any high numbers of patients (17%) operated on for emergency perforation.

So I think that if you are going to compare the early operative mortality in any of these series, you have got to look at a lot of different factors that influence outcome.

Dr. R. K. Gilchrist (Chicago): In the first some 250 two-thirds resections I did with Billroth II up to the mid-50's, the only recurrences we had in three years were those who started smoking heavily. In most of those, their recurrence healed if you could get them to stop smoking.

I wonder whether this is an accident, whether I was too much impressed by it, or whether the rest of you have noticed this.

DR. EDWARD R. WOODWARD (Closing discussion): In reply to Doctors Herrington and Griffen, I think there is a partial explanation in that we use a very different method of selection. We use vagotomy and antrectomy in our patients where peptic ulcer recurrence would be particularly likely or hazardous. For example, we would use this in the patient who has recovered from a massive hemorrhage. This explains why two-thirds of our patients treated by vagotomy and pyloroplasty have intractability as their indication. Their selection on the other hand has been based on the pathologic evidence that antrectomy would be unduly hazardous. It is of course well known that both these discussants are very strongly prejudiced in favor of vagotomy and antrectomy.

We recognize full well the advantages of vagotomy and antrectomy, as alluded to earlier by Dr. Thompson, and supported by the experimental studies reported some years ago by Dr. Paul Jordan. There is an important synergism between gastrin and vagal innervation, showing that a slightly incomplete vagotomy would no longer permit significant excitation of parietal cell activity after antrectomy. This explains the lower recurrence rate after vagotomy and antrectomy and in terms of disease control this is the most effective operation available today.

I do think that the practicing general surgeon has been drastically oversold on the use of vagotomy and antrectomy. A substantial majority of these surgeons feel *compelled* to perform antrectomy in addition to vagotomy regardless of the pathology presented by the individual patient. This results, as expected, in a high mortality related to dehiscence of duodenal closures, leaking anastomoses, obstructed outlets, et cetera. There is absolutely no doubt that the simpler procedure of truncal vagotomy and pyloroplasty is infinitely safer and should be used much more widely than it is at present.

Dr. Irwin somehow got erroneous data on our mortality for emergency surgery. We had only a 1.8% mortality with one death in 38 patients who were in shock from hemorrhage. We feel very strongly that the approach illustrated years ago by Dr. Jack Matthew Ferris, with immediate pylorotomy, suture ligation of the bleeding ulcer, and then completion of pyloroplasty and vagotomy in the repleted patient, has been the most important forward step in this complication of duodenal ulcer in three decades.

Dr. Gilchrist, there is a close association between heavy smoking and peptic ulcer, as with a number of other diseased states. Most gastroenterologists agree that heavy smoking is deleterious and leads to recurrence following either medical or surgical therapy for peptic ulcer.

A Prospective Study of Parietal Cell Vagotomy and Selective Vagotomy-antrectomy for Treatment of Duodenal Ulcer

PAUL H. JORDAN, JR., M.D.

A prospective, randomized, study involving 92 patients who required elective operation for treatment of duodenal ulcer was performed to compare the results of Parietal Cell Vagotomy (PCV) and selective vagotomy-antrectomy Billroth I (SV-A-BI). The protocol was broken twice. One patient was unable to undergo PCV because of pyloric stenosis and one patient underwent Billroth II anastomosis instead of Billroth I because of post-bulbar stenosis. Performance of PCV was never aborted because a patient was obese. There were no deaths. Diarrhea, dumping and other gastric complaints were less frequenct after PCV than after SV-A-BI for all time periods studies up to two years. Two months after operation, the Hollander tests were negative in 59% of patients after PCV and in 100% after SV-A-BI. Inhibition of BAO and MAO were also significantly less after PCV than after SV-A-BI. Since vagotomy of the parietal cell mass was identical in both groups of patients it was concluded that the differences in the secretory rates and the fewer negative Hollander tests in the PCV group than in the SV-A-BI group were due to retention of the antrum irrespective of its innervation. There was no explanation for the gradual increase in the BAO in the PCV group. One recurrent ulcer occurred in the PCV group in a patient who overindulged in alcohol and aspirin. After 4 days of medical management, this superficial ulcer healed as demonstrated by endoscopy. There were no recurrent ulcers after SV-A-BI. As a result of this study, it is concluded that PCV is superior to SV-A-BI because of the lower frequency of postoperative complications, diarrhea, dumping and other symptoms associated with gastric surgery. PCV may be the operation of choice for the elective treatment of duodenal ulcer; however, it remains undetermined whether the recurrent ulcer rate following PCV will be sufficiently low that the procedure can retain a position of superiority over SV-A-BI.

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GRIFFITH AND HARKINS[4] recognized that ablation of the pyloric sphincter contributed significantly to the undesirable sequelae of gastric surgery. They studied, in dogs, the possibility of performing a vagotomy of the acid secreting portion of the stomach which at the same time preserved the innervation of the antrum so that destruction or bypass of the sphincter to permit gastric emptying was unnecessary. This logical concept lay fallow until Holle[7] first performed in man Selective Proximale Vagotomie which he combined with pyloroplasty. The full potential of Griffith and Harkins'[4] proposal was not realized clinically until Johnston[10] reported that patients undergoing highly selective vagotomy did not require a drainage procedure so long as the pyloric lumen was not severely compromised by fibrosis and obstruction.

Subsequently this operation was performed by many surgeons and the results obtained by those authors[2,18] with the greatest experience have been excellent. In comparison with other gastric procedures dumping and diarrhea were reduced in frequency and severity and the number of persistent or recurrent ulcers was astonishingly low. Other authors[16,21] with fewer patients reported an alarming number of recurrent ulcers but as their experience increased, the frequency of recurrent ulcers decreased.[17,22]

The attractive physiological features of parietal cell vagotomy and the good results obtained by Johnston[10]

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TABLE 1. *Preoperative Data Pertaining to Ulcer Patients*

	PCV (N = 45)	SV-A-B_I (N = 47)
Duration of Ulcer Symptoms (Years)	10 ± 7	13 ± 7
Patients with history of bleeding	17	19
Patients requiring transfusions	6	3
Patients with previous perforation	4	10
Patients with UGI Roentgenograms	42	47
Those + for ulcer crater	23	23
Those suggestive of ulcer	19	23
Number of Patients Gastroscoped	31	31
Gastroscopy + for ulcer	28	23
Gastroscopy suggestive for ulcer	3	2

± = Standard deviation

and Amdrup[1] encouraged us to perform a pilot study to determine whether, in our hands, the operation warranted a prospective, randomized evaluation. The early results that were obtained in 35 patients demonstrated that the operation could be performed in the majority of patients treated for intractability.[11] On the basis of the good early results obtained in that study a prospective, randomized study was initiated to compare parietal cell vagotomy without drainage (PCV) and selective vagotomy, antrectomy and Billroth I anastomosis (SV-A-BI). This operation was chosen for comparison because the frequency of postoperative, gastric, sequelae associated with its use was no greater than with other procedures and the number of recurrent ulcers was less than with any other procedure.

Patients and Methods

Ninety-two consecutive patients requiring elective operation for duodenal ulcer were studied. Cases accrued to the study between April, 1973 and October, 1975. No patient with known obstruction or active bleeding was entered into the study. The operation to be performed was selected randomly prior to opening the abdomen. It was necessary to deviate twice from the operation selected. One patient underwent a resection and a Billroth II anastomosis instead of PCV because the pylorus was deemed too constricted. In one patient, a Billroth II anastomosis was performed because it was considered a safer procedure than a Billroth I anastomosis. The operations actually performed were PCV in 45, SV-A-BI in 45 and SV-A-BII in two patients. Three patients undergoing SV-A-BI had stomal dysfunction and required gastroenterostomy. All patients were symptomatic at the time of operation.

Although duodenal ulcer disease was the principle indication for operation, additional operative procedures performed at the time of PCV included splenectomy in 4 patients, appendectomy in 10, hiatal herniorrhaphy in 2, left hepatectomy in 1, aorto bilateral-femoral by-pass graft in one and gastrotomy in 7 patients to verify the existence of a duodenal ulcer. The pylorus was narrowed in two patients but was adequately dilated in one patient to permit PCV without drainage. In the second patient it was necessary to perform resection instead of PCV. There was marked periduodenal inflammation present in 17 patients and 6 patients were very obese. in the patients undergoing SV-A-BI, splenectomy was performed in 3 patients and appendectomy in 8. The pylorus in 3 patients assigned to this operation would have been too small to permit PCV had this operation been selected. There was marked periduodenal induration and inflammation present in 9 patients.

The duration of ulcer disease prior to operation and the number of patients with a history of bleeding or previous perforation are presented in Table 1. Although some patients were bleeding when admitted to the hospital, none was bleeding at the time of operation and all were able to undergo gastric analysis. An ulcer crater was demonstrated in 52% of 89 patients studied roentgenographically and in 90% of 62 patients examined gastroscopically.

The author participated in all operations reported in this study. The technique of PCV employed was similar to that previously published.[12] The junction between the fundic and pyloric gland areas of the stomach was located by noting where the main terminal branch of the anterior nerve of Latarjet approached the lesser curvature of the stomach. This point averaged 6 cm from the pylorus. The main vagal trunks were isolated with tapes because gentle traction on these tapes facilitated the dissection and helped to avoid injury to the nerves of Latarjet. The lesser curvature was then devascularized from the antral-fundal junction to the esophagogastric junction. The esophagus was completely encircled in order to facilitate its inspection and section of all vagal branches to the stomach. The terminal esophagus was mobilized and anything suggestive of a nerve structure that appeared to come from the main vagal trunks and was supplying the distal 4 cm of esophagus was cut. The operation was completed by performing reperitonealization of the lesser curvature of the stomach and suturing the phrenoesophageal ligament attached to the esophagogastric junction to the diaphragm.

In those patients undergoing antrectomy vagotomy was done exactly as in those patients who had PCV alone. It was by this means that the size of the antrum was estimated. After vagotomy the antrum was resected using the line between innervated and denervated stomach as the line of transection. The portion of stomach removed was not more than 20% of the stomach and was smaller than our estimate of the antrum in previous studies. The lesser curvature of the stomach was closed and a gastroduodenostomy performed. The proximal margin of the specimen was consistent with the transitional zone or of the antrum but not of the fundic area.

Gastric secretory studies were performed preoperatively and at 2, 6, 12 and 24 months postoperatively on those patients who would consent. The technique for the secretory studies was previously reported.[11] Maximal acid output (MAO) was stimulated by the administration of 1.2 mg of Histalog (Betazole) per kg. Gastric juice was collected in 15 minute periods for two hours. The insulin acid output (IAO) was performed by administration of 0.2 u per kg of regular insulin. Gastric juice was collected in 15 minute periods for two hours. In the basal period (BAO) preceding each test gastric juice was collected for four consecutive 30 minute periods. An aliquot of each collection of gastric juice was titrated with 0.1 N sodium hydroxide to pH 7.3 and the total two hour acid output for each test calculated. The acid secretion for the first and second hours after insulin stimulation was calculated also. Hollander's[6] criteria for interpretation of the test were applied to each hourly sample, to determine if the insulin test was early or late positive. The peak hourly basal, Histalog and insulin stimulated acid outputs were also expressed as PAO_B, PAO_H and PAO_I, respectively. These values were determined by taking the two successive 15 minute periods showing the highest acid output in the respective tests and multiplying by two.

Gastric analyses performed preoperatively were of limited value in establishing a diagnosis or in making the decision whether or not to operate. Very high basal acid output suggested on several occasions the coexistence of a gastrinoma. In these patients, the effects of the calcium challenge and the secretin challenge tests on acid secretion and serum gastrin levels were studied. A gastrinoma was not identified in any patient.

Efforts were made to readmit patients to the hospital for studies and interview at 2, 6, 12 and 24 months. In addition to a standard set of questions asked at each time period by the author, any suggestive response was pursued in depth. Many of the patients were also interviewed at one year by an independent physician. Upper gastrointestinal roentgenograms were made prior to discharge from the hospital after operation and at the time of study two months after operation. Subsequently, roentgenograms were made only in those patients who had retention of barium at the time of the previous examination or in whom it seemed clinically indicated. Patients underwent gastroscopy whenever they had any gastric complaints that at all resembled recurrent ulcer.

A provocative dumping test was performed by administration of 250 ml of ½ and ½ cream and milk and 100 ml of 50% dextrose. A nasogastric tube was placed into the stomach to test for overnight gastric residual and before it was removed, the "dumping cocktail" was introduced through the tube without the patient knowing what was given. The patients were then observed for two hours and changes in pulse rate and blood pressure, the occurrence of flushing, sweating, headache, borborygmi and the urge to defecate were recorded at 15 minute intervals. This test was performed in 13 patients in whom there was a question of dumping.

The method of grading the clinical results was a simplification of the Visick grading system proposed by Kennedy[14]; **I** no symptoms, **II** mild but not troublesome symptoms, **III** more severe symptoms with some disability, **IV** disabling symptoms or recurrent ulcer.

TABLE 2. *Major Complications Associated with Operation*

	Number of Patients	
Complication	PCV	SV-A-B_I
Wound infection	2	3
Stomal dysfunction	1	7
Reoperation for stomal dysfunction	0	3
Reoperation for intestinal obstruction	2*	2†
Average days hospitalized postop	10 ± 3	13 ± 8
Hospitalization longer than 10 days postop	11	25
Two hour gastric retention of barium at discharge	11/44	25/46
Two hour barium retention at 2 months	4/41	8/39

* One at 10 days and one 6 months after PCV
† Both at 12 months after SV-A-B_I
± = Standard deviation

Results

Immediate Postoperative Results: There were no operative deaths in the study. After PCV the nasogastric tube was usually removed the day of or the day after operation and feedings were started by the third day. Removal of the nasogastric tube and resumption of feeding were delayed by several days after antrectomy. The average number of hospital days required after PCV and SV-A-BI were 10 and 13, respectively.

Early postoperative complications related to operative technique are summarized in Table 2. There were no anastomotic leaks recognized. Seven patients had stomal dysfunction after SV-A-BI. None of these patients had an associated febrile episode to suggest infection or abscess and only one patient had a second procedure (appendectomy) done at the first operation. Three of the 7 patients required reoperation. The anastomoses were patent but had failed to function properly because of surrounding fat necrosis. This was due to pancreatitis in one patient in whom the resection and the anastomosis had been difficult. A gastrojejunostomy was performed in each of these three patients with complications. One of these patients was subsequently reoperated for small bowel obstruction. The

TABLE 3. *Patients Available for Study*

Operation	Patients	Preop	Months Postop 2	6	12	24
PCV	Interviewed	45	41	34	27	12
	Studied	45	39	32	24	12
SV-A-B$_I$	Interviewed	47	42	33	26	13
	Studied	47	38	29	17	9

induration surrounding the Billroth I anastomosis had completely disappeared.

Initially one patient had prolonged gastric retention after PCV. The pylorus was widely patent on gastroscopy but gastric motility was diminished. This problem disappeared within two months and was attributed to possible injury to the anterior vagus nerve. Two patients required reoperation for intestinal obstruction after PCV and two after SV-A-BI. No patient in the PCV group required reoperation for pyloric obstruction.

Late Followup Studies: The number of patients interviewed and who consented to study at the various time periods after operation appear in Table 3. Of the PCV patients, two died at one year and one at two years. After SV-A-BI, one patient each died at 6, 12 and 24 months. No death was related to duodenal ulcer disease or to the operation. The postoperative gastrointestinal complaints elicited from patients are tabulated in Table 4. Abdominal discomfort referred to symptoms that might suggest recurrent ulcer including distension, gas and any other nondescript symptoms. Because of these symptoms, 6 patients underwent gastroscopy after PCV and one patient after SV-A-BI. Evidence of a recurrent ulcer was noted at one year in one patient after PCV. Many patients acknowledged early satiety and mild dysphagia during the first postoperative month after both operations but these complaints had greatly diminished by the second month.

TABLE 4. *Postoperative Gastrointestinal Symptoms*

	PCV Months 2	6	12	24	SV-A-B$_I$ Months 2	6	12	24
Number of Patients Studied	41	34	27	12	42	33	26	13
Symptoms								
Early satiety	2	1	0	0	4	3	0	0
Early dumping	6	6	2	2	13	8	8	7
Late dumping	1	1	0	0	4	3	3	1
Dysphagia	3	1	2	0	3	0	0	1
Nausea	1	0	0	0	0	2	0	0
Vomiting	0	0	0	0	0	2	0	0
Epigastric discomfort	0	0	2	2	0	1	2	0
Diarrhea	2	0	0	0	3	3	2	1
Reflux	2	0	1	1	1	0	1	1
Number of Patients Without Symptoms	25	25	20	8	20	19	15	6

The frequency of dumping was greatest two months after operation and occurred in 15% of patients after PCV and 31% after SV-A-BI. Of the patients with early dumping at two months who were studied for two years, dumping persisted throughout that period in 2 of 4 patients with PCV and in 4 of 6 patients after SV-A-BI. Dumping was not incapacitating for any patient but it was of greater magnitude after SV-A-BI than after PCV. Dumping that occurred after PCV could be easily controlled by the elimination of milk, chocolate or high carbohydrate foods. The dumping test was performed with negative results in one of the two patients with dumping after PCV. It was performed in 4 of 6 patients with persistent dumping after SV-A-BI. The test was positive in each of these 4 patients and resulted in tachycardia, nausea, flushing and passage of a loose bowel movement.

At two months diarrhea, unrelated to dumping, occurred in two patients with PCV but was continuous in neither patient after that time. After SV-A-BI, three patients had diarrhea at two months but it persisted throughout the study in only one patient. The severity of diarrhea was also greater after SV-A-BI than after PCV; however, it was not disabling or of serious consequence for any patient.

Secretory Studies: Table 5 shows the range of acid recovered during the two hour preoperative basal secretory tests. The number of patients secreting at different rates were distributed approximately equally in the two groups; although, there were more of the very low secretors in the PCV group and more of the very high secretors in the SV-A-BI group. Table 6 shows the change in secretory rates with time and the per cent that the secretory rates at the various time periods were inhibited when compared with the preoperative secretory rates. After SV-A-BI, all secretory parameters were inhibited in excess of 85% at all time periods when compared with the values for the same parameters measured preoperatively. The results after PCV were quite different. With time, there was a steady rise in the basal and

TABLE 5. *Preoperative Basal Secretory Rates*

mEq HCl Per 2 Hr	Per cent Patients PCV	SV-A-B$_I$
0– 2	11	6
2.1– 4	18	21
4.1– 6	12	21
6.1– 8	16	19
8.1–10	20	6
10.1–20	16	11
>20	7	15

TABLE 6. *Results of Gastric Secretory Studies*

		PCV Months Postop					SV-A-B$_I$ Months Postop			
	Preop	2	6	12	24	Preop	2	6	12	24
Mean PAO_B mEq/hr	6.1	1.2	1.9	2.5	2.3	7.2	0.2	0.4	0.3	0.4
Mean PAO_H mEq/hr	44.9	16.4	15.9	18.7	16.8	42.4	4.9	5.1	3.8	3.4
Mean PAO_I mEq/hr	34.9	2.2	3.2	4.6	4.6	35.8	0.2	0.1	0.5	0.3
% Reduction:										
PAO_B		81 ± 34	63 ± 29	55 ± 40	53 ± 24		98 ± 7	86 ± 28	97 ± 4	95 ± 3
PAO_H		60 ± 16	63 ± 17	51 ± 15	54 ± 15		88 ± 8	86 ± 15	90 ± 7	92 ± 3
PAO_I		86 ± 8	89 ± 8	87 ± 11	88 ± 3		99 ± 1	99 ± 1	99 ± 1	99 ± 1
Mean BAO mEq/2 hr	8.3	1.5	2.6	3.3	4.0	9.6	0.2	0.4	0.4	0.3
Mean MAO mEq/2 hr	72.1	24.6	25.6	29.7	30.4	69.0	6.3	6.3	5.1	3.5
Mean IAO mEq/2 hr	45.6	2.6	2.4	6.1	6.4	44.8	0.1	0.6	0.4	0.3
% Reduction:										
BAO		81 ± 28	67 ± 33	56 ± 35	44 ± 30		95 ± 10	92 ± 25	97 ± 5	92 ± 4
MAO		64 ± 17	63 ± 18	57 ± 19	55 ± 17		90 ± 10	88 ± 12	92 ± 6	94 ± 4
IAO		89 ± 9	88 ± 14	87 ± 7	89 ± 6		99 ± 1	99 ± 1	98 ± 1	99 ± 2
Patients Tested	45	39	32	24	12	47	38	29	17	9

± = Standard deviation

maximal acid secretory parameters so that after two years basal and maximal acid outputs were approximately 50% of the preoperative values. At two years the inhibition of BAO was significantly ($P < 0.05$) less than it had been at two months. There was no other significant difference in the degree of inhibition between any two time periods for any of the secretory parameters. Inhibition of the acid response to insulin was more persistent and was 80% at two years compared with 86 to 89% at two months.

After PCV the per cent of patients with a negative insulin test decreased from 59% at two months to 33% at 24 months (Table 7) although the acid secretory response to insulin was inhibited nearly the same at both time periods (Table 6). By contrast, the acid response to insulin after SV-A-BI was almost completely inhibited at two months and remained so throughout the two years. After SV-A-BI all patients had a negative insulin test at two months and there was little indication of a decreasing number of negative tests with time.

At all time periods, the per cent of patients who had returned to full employment was greater after PCV than after SV-A-BI (Table 8). The postoperative work record of those patients undergoing PCV was better than those who had SV-A-BI even when one considered that more patients in the PCV group were working preoperatively.

Table 9 shows the changes in the patients' weight compared with their preoperative weight. At each time interval the per cent of patients who equaled or exceeded their preoperative weight was greater after PCV than after SV-A-BI.

Evaluation of Patients

Recurrent Ulcers: The one recurrent ulcer that developed in the study occurred in a man 12 months after PCV. He had been well until Christmas when he imbibed heavily in alcohol and aspirin. He complained of epigastric pain and gastroscopy confirmed a small superficial duodenal ulcer. His insulin test was positive. The patient was treated medically and when he was regastroscoped 4 days later the ulcer had healed. The patient has been without symptoms for a year. No patient was a possible suspect for recurrent ulcer at the time of this report.

The grading of the clinical results is seen in Table 10. While both operations provided overall good results, 4% of patients at one year had results that fell outside of the excellent or good categories following PCV and 15% had

TABLE 7. *Results of the Hollander Tests*

	PCV Months Postop				SV-A-B$_I$ Months Postop			
Number of Tests	2	6	12	24	2	6	12	24
Negative	23	13	4	4	38	27	15	9
Early Positive	6	9	12	6	0	0	0	0
Late Positive	10	11	8	2	0	1	2	0

TABLE 8. *Work Status of Patients After Operation*

	PCV Months Postop					SV-A-B$_I$ Months Postop				
	Preop	2	6	12	24	Preop	2	6	12	24
Full Time	32	14	23	21	8	29	9	18	15	5
Part Time	1	3	2	1	1	2	3	3	1	1
No Work	12	24	9	5	3	16	28	12	10	7
Per cent Working Full Time	71	34	68	78	67	62	23	55	58	38

results that failed to achieve the excellent or good categories after SV-A-BI. If one considered the shorter postoperative recovery time, fewer significant complications and an intangible sense of well-being manifested by work and weight status associated with PCV, the difference between the two operations might be greater than the results of the Visick grading indicated.

Discussion

Parietal cell vagotomy without a drainage procedure has been practiced for nearly 8 years. The reported results of the operation have been generally enthusiastic although a few early reports on small numbers of patients provided a cautious warning regarding the overzealous adoption of the operation. This paper confirms the favorable reports and suggests that for at least two years PCV is equally as effective as SV-A-BI in the prevention of recurrent ulcer and is superior to that operation with respect to the fewer postoperative complications and gastric sequelae that occur.

The severity of the duodenal ulcer diathesis was nearly equal in both groups of patients in terms of symptomatology, acid secretion and existing pathology. Preoperative verification of duodenal ulcer was significantly more accurate when made by endoscopy using the flexible gastroscope than by roentgenograms. This method of examination was a valuable tool not only for diagnosis but for postoperative evaluation of patients' symptoms. Therefore, endoscopy must be easily accessible to the surgeons trained in its use. It is no more logical for the gastroenterological surgeon to be denied the use of this diagnostic modality than it would be for the thoracic surgeon to be restricted in the use of the bronchoscope.

TABLE 9. *Weight Change in Patients After Operation*

	PCV Months Postop				SV-A-B$_I$ Months Postop			
	2	6	12	24	2	6	12	24
No. of Pats.	40	34	26	12	42	30	24	12
> Preop Weight	5	8	8	6	6	5	6	2
= Preop Weight ± 6.6 Kg	13	9	11	2	9	9	2	1
< Preop Weight	22(5)*	17(3)*	7	4	27(7)*	16(3)*	16(3)*	9(1)*
Per cent Equaled or Exceeded Preop Weight	45	50	73	67	36	47	33	25

* Number of patients below ideal weight

It has been stated that PCV is a time consuming operation and that its application is limited, particularly in obese patients. In the average patient, the time required for PCV equaled that for truncal vagotomy and pyloroplasty. We were able to perform PCV in 45 of 46 patients assigned this operation for elective treatment of duodenal ulcer irrespective of the fact that 6 were extremely obese. In the one patient in whom PCV was not performed, the pylorus was considered too constricted and unsuitable for dilatation. The operation does require a longer time and is more difficult when the patient is obese. One can obviously perform truncal vagotomy with greater facility in these patients and it is always an option that is open to the surgeon. However, to persist with PCV in a difficult patient must be based on the surgeon's conviction that PCV provides an advantage to the patient. Then it will not be difficult for him to spend the extra time and effort required to perform the operation correctly. In fact, if the surgeon has not been convinced of its merits, he should not embark on PCV.

During the first two postoperative months, gastric retention of ingested barium after SV-A-BI was greater than after PCV. The degree of barium retention noted after SV-A-BI was unexpected since we had never performed upper gastrointestinal roentgenograms routinely in the early postoperative period before. Whether this finding was of clinical importance is doubtful since the patients did not complain of retention with the same frequency and by the sixth month roentgenograms failed to demonstrate retention. It is of interest, however, that 7 of 13 patients with early dumping during the first two months after SV-A-BI and 2 of 6 patients following PCV also had early barium retention. The explanation for greater barium retention after SV-A-BI than after PCV was probably related to stomal function rather than stomal patency for a number of patients with retention were gastroscoped and the stomas were completely patent. Three patients, however, were reoperated and a gastroenterostomy performed because of stomal dysfunction and external compression by a sterile inflammatory mass. These patients might not have required reoperation had we been willing to wait longer for the anastomosis to function. This was suggested in 2 of the 3 patients by the subsequent roentgenograms that demonstrated gastric emptying through the gastroduodenostomy as well as the gastrojejunostomy.

This study confirmed previous reports showing that the incidence of dumping[2,8] was less after PCV than after other operations in which the pylorus was by-passed or destroyed. At the two month followup period dumping occurred in 15% of patients after PCV and 31% after SV-A-BI. At one year dumping had decreased to 7% in patients with PCV but remained at 31% in those who had SV-A-BI. Dumping after PCV was always mild and could be easily avoided by the elimination of a particular item from the diet, usually sweet milk. Buttermilk or a small amount of sweet milk on cereal and in cooking was tolerable. Drinking a glass of sweet milk, however, would cause dumping. Since liquids leave the stomach more quickly than normal after PCV the problem arising with milk may be due to the rapid exodus of milk from the stomach and a relative lactase deficiency.[19] Dumping after SV-A-BI was usually more difficult to control than after PCV and was a serious problem in one patient. In several retired patients dumping would have created a greater problem had they been working for then it would have been difficult or impossible for them to lie down after eating.

As in other studies,[2,9] diarrhea occurred infrequently after PCV. Two months after PCV diarrhea was present in two patients but persisted in neither. After SV-A-BI diarrhea was present in three patients at two months and persisted in the one patient who has been followed for two years. Of particular interest are two patients who had previously had a right colon resection. The bowel pattern in the patient undergoing PCV was only slightly altered from what it had been preoperatively; however, the bowel movements of the patient who underwent SV-A-BI increased in frequency and were of a watery consistency. The difference between these two patients suggested that the preservation of the pyloric sphincter was of particular benefit to the patient in whom the ileocecal valve had also been lost.

The results of this study were too premature to draw conclusion concerning the relative frequency with which recurrent ulcers will develop after the two operations. The only recurrent ulcer after either operation occurred one year after PCV as a complication of alcohol and aspirin ingestion. After 4 days on medical treatment, endoscopy demonstrated that the ulcer had healed. A satisfactory reduction in BAO or MAO was not achieved in this patient and the insulin test had changed from a late to early positive. The patient demonstrated that while the secretory response after PCV was sufficiently reduced to permit healing of an ulcer, the operation did not protect the stomach or duodenum from the abuse of excessive ingestion of alcohol and/or aspirin. Under these stresses, the stomach, capable of acid production after PCV, is subject to the development of a peptic ulcer as might occur in anyone. Although recurrent ulcers after PCV have been reported as low as 2%,[2,15] the persistence of a significant basal acid secretion reported by others[3] and our observation that it increased with time gives us concern that the recurrence rate after PCV may increase.

TABLE 10. *Evaluation of Clinical Results*

Evaluator	Operation	Months Postop	Patients Studied	Per cent Visick I	II	III	IV
Patients and Author	PCV	2	41	39	2	0	0
		6	34	30	4	0	0
		12	27	23	3	0	1
		24	12	9	3	0	0
	SV-A-B$_\text{I}$	2	42	31	8	3	0
		6	33	25	8	0	0
		12	26	16	6	4	0
		24	13	8	4	0	1
Independent Observer	PCV	12	24	18	6	0	0
	SV-A-B$_\text{I}$	12	20	13	7	0	0

The decreased secretory response to insulin and the fewer patients with a positive Hollander test after SV-A-BI than after PCV could be attributed to compensation for incomplete vagotomy of the parietal cell mass by antrectomy. If this was the explanation, why should the insulin response and the number of positive Hollander tests increase with time after PCV but not after SV-A-BI? These observations might be explained by reinnervation of the parietal cell mass. Since the vagotomy of the parietal cell mass was identical in both groups of patients, one would have to assume that reinnervation of the parietal cell mass occurred via the retained vagal fibers to the antrum. The marked differences in the acid secretory rates after the two types of operation leave one with the inescapable conclusion that the explanation is related to the retention of the antrum or its innervation in one group and not the other. Similar differences in acid secretory rates were observed after truncal vagotomy, antrectomy and Billroth I and truncal vagotomy and pyloroplasty.[13] It is, therefore, our opinion that the differences noted in the secretory patterns between SV-A-BI and PCV were due to retention of the antrum rather than retention of its innervation. One can speculate that the greater response to insulin after PCV than after SV-A-BI was due to a non-vagal effect of insulin, perhaps the effect of insulin released catecholamines on gastrin release.[5,20] This does not explain, however, why the basal secretory response after PCV increased with time. The hypothesis that there is reinnervation of the parietal cells which makes them more sensitive to gastrin from the retained antrum remains a possibility.

Prospective studies performed to evaluate different operations for the treatment of duodenal ulcer have shown that, with the exception of an increased number of recurrent ulcers after vagotomy and drainage operations, there has been a surprising similarity in the frequency of gastric symptoms observed in patients who have undergone different operations. Our study showed that it was technically possible to perform PCV in 95% of patients undergoing elective operation. The early symptomatic results of SV-A-BI were good but those following PCV were better. The question to be answered before PCV can be recommended for general use without reservations is whether the recurrent ulcer rate after 5 to 10 years will fall within an acceptable level. While this study did not contribute to the final answer to that question, our results along with others were encouraging in a negative way since recurrent ulcers did not develop as a problem during the period that the patients were studied.

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DISCUSSION

DR. EDWARD R. WOODWARD (Gainesville, Florida): We share Dr. Jordan's guarded enthusiasm for this procedure, and have used it both in a series of randomized patients, in association with three other southern universities, and also have used it in selected cases—those I call the disaster-prone patients. This, in general, is the white, middle-aged female with intractable duodenal ulcer. In our early experience, we discovered in Chicago that in the first 500 cases women accounted for only 10% of the operations, but they accounted for 50% of the bad results. In this particular group we have found PCV to be delightfully well accepted, and very pleasantly free of postoperative sequelae.

We had difficulty in mastering the technique until one of us visited Leeds and watched Goligher and Johnston operate. They use what my house staff refer to as the "automatic intern," and I can recommend this for any parahiatal surgery. This is a subxiphoid retractor attached to a rigid standard on the edge of the table, with the patient then put in reverse Trendelenburg. This flattens out the diaphragm, makes exposure at the e.g. junction much easier, and even, to some extent, straightens out the lesser curvature, making dissection of these tiny fibers under direct vision much easier.

We have had in 25 patients one recurrent duodenal ulcer. I would like to ask Dr. Jordan how to overcome the difficulties in the surgical management of recurrence after this operative procedure.

DR. THOMAS BOMBECK (Chicago): I rise to discuss this paper as one of those people who has had one of these small series, which we have been brash enough to present early on. That's especially significant in view of the results of this particular series. This is one of the very few and possibly the first very good randomized series of this operation which demonstrates a good, acceptable result. I would first like to address myself to the possible reasons for that.

(Slide) This slide was first presented a year ago at the Surgical Forum. It demonstrates the results of basal and augmented, or augmented histamine and basal secretory studies in patients with parietal cell vagotomy alone, selective vagotomy-antrectomy, and truncal vagotomy, studied preoperatively, six weeks postoperatively, and one year postoperatively. The dashes here represent patients with parietal cell vagotomy. This demonstrated exactly the same sort of result that Dr. Jordan and others have presented that parietal cell vagotomy does not result in gastric secretory levels although it results in an early fall. The basal and the augmented histamine secretory levels do recover, although in his series they did not recover to anywhere near preoperative levels. In our series they did.

This was presented on 14 patients in the parietal cell vagotomy series, and at that time we had two recurrent ulcers. That was an incidence of approximately 14%. Other authors doing randomized series, Amdrup with 8%, Wastell with 16%, Kronborg with 22% in their early randomized series, had suggested that perhaps it was premature to be investigating this operation. So the question arises: What's different about our series and about Dr. Jordan's series?

I think the answer lies in the technique used. Technique is all-important in parietal cell vagotomy, simply because one is not protected from one's sins by an antrectomy; so that if you leave any degree of parietal cell innervation with parietal cell vagotomy, you will have a high secretory value postoperatively. Perhaps Dr. Jordan will review again the upper and lower extent of his operations. I think they are rather larger than most other people's.

Now, Dr. Jordan reported one recurrence, saying that that patient had a somewhat abnormal secretory pattern. I would like to know what the secretory values were on that particular patient.

The operation itself has redefined the requirements for a successful ulcer operation. Patients don't have to be resting achlorhydric, or have interdigestive achlorhydria, following parietal cell vagotomy. Total acid secretory ablation isn't necessary to adequately treat a duodenal ulcer. It hasn't answered the question, however, how much secretory ablation is necessary in this particular situation. I wonder if Dr. Jordan could address himself to that.

Dr. Jordan has suggested that perhaps the operation is ready. I wonder about that, because he's got only two years' followup in his series. Other people have somewhat the same, except those with high recurrence rates, and it seems to me that we'd be a little premature at this point in recommending that the operation be applied clinically, although you might make the statement that the increased recurrence is worth the lack of complications that you get.

Dr John L. Sawyers (Nashville): We too share Dr. Jordan's enthusiasm for parietal cell vagotomy.

As Dr. Woodward said, we are one of the cooperating universities in the South that have been doing prospective randomized studies with parietal cell vagotomy. While the results of that cooperative study have not yet been compiled, I have seen enough two-year results reported that I feel justified in showing you two slides from the experience of the Nashville group.

(Slide) Dr. Lynwood Herrington has been randomizing truncal vagotomy and antrectomy against parietal cell vagotomy, and this is the report of his studies after two years. Thirty-eight patients have been in the truncal vagotomy-antrectomy group; 36 in the parietal cell vagotomy group, with no mortality in either, and there have been no recurrent ulcers. Dumping, mild to moderate, has occurred in 20% of the truncal vagotomy and antrectomy group, which is consistent with the percentage of dumping that we have found in the much larger series of over 3000 patients. There has been no dumping in the parietal cell vagotomy group. Mild diarrhea in 10% of the truncal vagotomy and antrectomy group, again consistent with the much larger group's incidence of diarrhea; only one patient in the parietal cell vagotomy group had diarrhea. No weight loss in either series. there has been a temporary postprandial fullness, lasting up to approximately two months with two of the patients in the antrectomy group, and in one third of the group following parietal cell vagotomy.

(Slide) I have been randomizing selective gastric vagotomy and Finney pyloroplasty against parietal cell vagotomy, and this is a two-year followup: 31 patients in the selective vagotomy and pyloroplasty group; 32 in the parietal cell vagotomy; no mortality in either, and no recurrent ulcer in either; dumping, 25% following the selective vagotomy and pyloroplasty, consistent with our findings whenever the integrity of the pylorus has been violated; only one patient in the parietal cell anatomy has very mild dumping; diarrhea, one following the selective vagotomy and pyloroplasty; none after the parietal cell vagotomy.

So on the basis of these admittedly very preliminary results, we are enthusiastic about this new operation of parietal cell vagotomy. I would add one note of caution, which has been mentioned by others, and that is on the technique of the procedure. I think this accounts for the early failures reported by Kronberg and others. The dissection must be carried well up above the esophagogastric junction.

Professor Grassi has pointed out that there are fibers from the posterior vagal trunk innervating the fundus of the stomach, which comes up well above the esophagogastric junction. He calls these vagal fibers "the criminal nerve." It's easy to overlook this nerve unless one carries the dissection up—we think it should be 5 cm—above the esophagogastric junction.

Dr. Raymond W. Postlethwait (Durham, North Carolina): I want to echo somewhat Dr. Bombeck's note of caution. Dr. Jordan very kindly allowed me to read the manuscript of his excellent study. If I am not mistaken, this is the first formal presentation of a randomized prospective evaluation of parietal cell vagotomy from this country. We should be grateful to Dr. Jordan for beginning his work so early, and showing us the progress to date.

Dr. Jordan in his paper alludes to the early enthusiastic reports, with which I'm sure you're all familiar. Although antrectomy and vagotomy results in a low ulcer recurrence rate, late sequelae remain in the range of 20–30%. Parietal cell vagotomy may reduce this, and be equally effective in the cure of ulcer.

The precise secretory studies reported by Dr. Jordan indicate, however, a gradual and significant return of acid secretion. This is disturbing, whatever the cause, and emphasizes the necessity for a cautious approach, by controlled investigations, of the parietal cell vagotomy before its wide acceptance.

Dr. Frank C. Spencer (New York, New York): Between two and three years ago, Dr. Kenneth Eng in our Department of Surgery at New York University was able to spend several weeks with Dr. John Goligher's department in Leeds, England and Dr. Amdrup in Copenhagen. Since that time Dr. Eng has carefully studied the effects of parietal cell vagotomy in a group of 30 selected patients and has been quite pleased with the results to date.

I rise primarily, however, to mention three points that may be of interest to our organization that were observed during a visit by the Society of Clinical Surgery this past September in Great Britain, spending one day with Sir Andrew Kaye's surgical department in Glasgow and a subsequent day with Dr. John Goligher's department in Leeds. The three points, partly alluded to by the previous speakers, seem quite pertinent to the concept of selective vagotomy. First, while watching Dr. Goligher perform such an operation, the unusually clear exposure obtained is clearly an important feature of the technique. Technical points included a reversed Trendelenburg position and a mechanical retractor on the sternum with mobilization of the terminal esophagus almost to the level of the skin. Certainly this wide mobilization and exposure greatly facilitated a very complete and precise selective vagotomy and is almost surely a significant factor in the good results they have consistently reported.

A second point was the five year followup data shown to our group by Dr. Goligher and his associates. As Dr. Jordan commented, there has been a return in gastric secretory activity in the first year; however with Dr. Goligher's serial studies, the return of activity has not subsequently progressed but has remained static with the degree of activity returning at one year, and remaining about the same at five years. This partial return of secretory activity has not been associated with a late recurrence of peptic ulcer.

A third important point, using the Visick grading technique as an index of morbidity, patients following a parietal vagotomy were far more free of side effects than any other operation which divided the pyloric sphincter, including such disability as diarrhea, bloating, transient pain, and the like.

One immediate application for the technique is that it may be the simplest operation to add to the closure of the patient with a perforated ulcer. This does not open the intestinal tract and in a certain percentage of patients is unnecessary, but the minimal morbidity would encourage its widespread use. We are currently investigating this approach at New York University.

A final word of caution, however; after endorsing Dr. Goligher's experience so enthusiastically, I was struck with the previous experience by comparison with a day's visit in Glasgow with Sir Andrew Kaye's surgical group. The procedure of parietal cell vagotomy was scarcely recommended with their preferred operation being vagotomy and gastroenterostomy!

Dr. Paul H. Jordan, Jr. (Closing Discussion): Dr. Woodward has mentioned the use of this operation for women. I agree that it is an ideal operation to use in a thin, little woman in whom the results with most gastric procedures are frequently very unsatisfactory.

We have reoperated upon only one patient for recurrent ulcer after parietal cell vagotomy. In that patient we did an antrectomy and a Billroth I. Interestingly, the acid secretory studies in that patient fell to zero after antrectomy. The mechanism for residual acid secretion after parietal cell vagotomy resides within the antrum. I don't think it's due to the preservation of the antrum's innervation because the identical thing happens when the antrum is resected after truncal vagotomy and pyloroplasty.

Dr. Bombeck has wondered why the results in our preliminary series seemed to be better than some of the other small series when initially reported. One reason may be that for a couple of years before doing parietal cell vagotomy we performed selective vagotomy using almost the same technique as is currently employed for parietal cell vagotomy.

Mr. Chris Wastell sounded an early warning note about recurrent ulcers when he reported recurrences in two of 16 patients. Dr. Kronborg from Copenhagen recently reported on 11 recurrences in 50 patients. Both investigators now feel that the recurrence rate is not nearly as high as suggested by these figures. Mr. Wastell in a recent report of 50 cases still had only the two earlier recurrences. Dr. Kronborg told me personally that his recurrent ulcer rate was 8% in 235 patients. He attributed this improvement in his recurrent ulcer rate to his visit to Leeds, England and his subsequent modification of his operative technique. There are several long term followup studies of sizeable groups of patients in which the proven recurrence rate is reported in the neighborhood of two to four percent and the proven and suspected rate is 5–8%. The combined study of Eric Amdrup and David Johnston is such a study although there have been three additional proven recurrences since their last report. I, therefore, do feel that evidence exists that the recurrence rate will be in the acceptable range when the operation is practiced by surgeons who are vitally involved in doing this operation correctly.

Dr. Postlethwait's proposed cooperative study will be very important because it will give us the opportunity to learn whether some of the good results that have been reported can be duplicated when the operation is performed by a group of good surgeons who are not so closely involved with this type of clinical investigation. The results of such a study may be indicative of the results that can be expected if the operation is adopted generally.

This question about total ablation of acid secretion is interesting. We as surgeons have in the past tried to totally ablate acid secretion because we have had no guides for selecting anything less than total ablation as a goal. I do not think it is necessary to ablate acid secretion totally to achieve good results and it may, in fact, not be desirable. In our first 35 patients we had a recurrent gastric ulcer in one individual who was taking 15 aspirin tablets a day because of a collagen disease. When that drug was withdrawn, he was placed on steroids. His ulcer healed and it has remained healed for two years in spite of the fact that he still has the capacity to make acid. This patient demonstrates that the presence of acid is not necessarily harmful and that no operation should be expected to protect the gastric mucosa from abuse.

The postprandial fullness after parietal cell vagotomy is a very common phenomenon. It occurs to some degree in almost every patient following parietal cell vagotomy or, for that matter, after almost any gastric operation for ulcer and is attributed to the loss of receptive relaxation after vagotomy. This complaint usually subsides and disappears in a short time after parietal cell vagotomy and is of no consequence. Our patients are told they can eat anything they want but that they should try to avoid overeating in the beginning.

It is very important that all nervous structures, whether they are called the "criminal nerve" of Grassi or the circumesophaegeal nerve, that appear to go to the esophagus, but in actuality go to the stomach, be cut. To ensure a good vagotomy, complete dissection and denervation of the terminal four centimeters of the esophagus is important.

Dr. Spencer raises the question about whether the degree of inhibition of acid secretion seen shortly after operation will persist for longer than one year. I think this is open to question. The Leeds group is of the opinion that the acid secretory rates do not change significantly after one year. This has not been our experience, for the degree of inhibition was less at two years than after one year. I thought this was unique with us but in talking with Dr. Jim Thompson I understand his experience has been similar. This continued rise in acid secretion noted by some of us is a cause for concern and requires careful observation to determine whether the continued rise in acid secretion is the exception or the rule.

Parietal cell vagotomy and simple closure is an ideal operation for a perforated duodenal ulcer. We have, in conjunction with Dr. Sture Hedenstedt, submitted a paper for publication describing the use of this procedure in patients with perforated ulcer whom we considered suitable candidates for definitive surgery. The operation provides protection for those who would have had further trouble with their ulcer but does not cause unpleasant sequelae in patients subjected to definitive surgery who might not have had further ulcer complaints.

Complications of Vagotomy in the Treatment of Hiatal Hernia

JOHN H. VANSANT, M.D., M.S. (SURG.), JOHN W. BAKER, JR., M.D.

Inclusion of vagotomy and pyloroplasty in the surgical treatment of gastroesophageal reflux associated with hiatal hernia has long been controversial. To evaluate the morbidity of vagotomy in the treatment of reflux esophagitis, a retrospective study of 311 patients treated by the Hill posterior gastropexy technique of hiatal hernia repair was tabulated. Vagotomy with the anti-reflux operation was performed upon 159 patients (51%). Vagotomy was not included for 152 patients (49%).

The incidence of postoperative symptoms with or without vagotomy was almost equally divided—41% without vagotomy and 47% with vagotomy. However, the major postoperative symptoms that occurred in both groups were abdominal cramps and bloating which usually disappeared in the early postoperative period and were attributed to the anti-reflux procedure and not to vagotomy.

When vagotomy was included with the anti-reflux operation, the incidence and duration of long term, disabling postoperative symptoms were significantly increased. Diarrhea occurred two times more frequently. Nausea and vomiting occurred ten times more frequently and dumping was present only in vagotomized patients.

Long term postoperative symptoms, judged on a basis of symptoms lasting longer than three months duration, occurred in 1% of patients without vagotomy and 26% when vagotomy was included.

This study revealed that no additional protection against recurrent symptoms of gastroesophageal reflux or radiographic evidence of recurrent hiatal hernia was provided by inclusion of vagotomy. In conclusion, vagotomy is contraindicated in the treatment of gastroesophageal reflux except in the presence of peptic ulcer disease.

From the Eastern Virginia Medical School, Norfolk, Virginia

IN 1967, a paper was published by the senior author[2] advocating adjunctive vagotomy and pyloroplasty in the surgical treatment of reflux esophagitis associated with hiatal hernia. This series of 35 patients revealed an incidence of 46% postoperative symptoms attributed to vagotomy. These symptoms included diarrhea, abdominal cramps and bloating, nausea and vomiting, and dumping. To evaluate the morbidity of vagotomy in the treatment of reflux esophagitis, a retrospective study of 311 patients treated by the Hill[1] posterior gastropexy technique of hiatal hernia repair was tabulated. Each patient was operated upon and followed by the senior author. Vagotomy with the anti-reflux operation was performed upon 159 patients (51%). In 152 patients (49%) vagotomy was not included. The four operative combinations are outlined in Table 1.

Results

Significant postoperative symptoms were observed in 136 patients (44%). In Table 2 the postoperative symptoms are tabulated in relationship to the operative procedure. The incidence of postoperative symptoms with and without vagotomy are compared in Table 3. Abdominal cramps and bloating were equal in the two groups; however, the incidence of diarrhea was twice as

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TABLE 1. *Operative Procedures*

Operation	No.	Per cent
Repair only	134	43
Repair with pyloromyotomy	18	6
Repair with vagotomy and pyloroplasty	118	38
Repair with vagotomy and resection	41	13
Totals	311	100

prevalent in the vagotomized group. Postoperative nausea and vomiting occurred ten times more frequently when vagotomy was included. Dumping syndrome occurred in 11 patients following vagotomy but did not occur with hiatal herniorrhaphy alone. There was a significantly higher incidence of persistent longterm (longer than 3 months) postoperative symptoms in patients who had vagotomy (Table 4). Postoperative symptoms were judged on a basis of duration rather than severity. Although the total incidence of postoperative symptoms was approximately equal in the two groups, only two (1%) of 152 non-vagotomized patients had symptoms longer than 3 months as compared with 41 (26%) of 159 patients in whom a vagotomy was included. The majority of the 41 patients with longterm symptoms had unrelenting diarrhea which was resistant to medical management.

Table 5 compares the duration of postoperative symptoms to the respective operative procedures.

In Table 6 the incidence of postoperative symptoms is tabulated according to the major indication for surgical intervention. In patients with uncontrolled esophagitis the incidence of postoperative symptoms was the same with or without vagotomy. The most significant increases in postoperative symptoms were associated with esophageal obstruction caused by symptomatic lower esophageal rings and strictures. In each category the incidence was three times higher when vagotomy was included.

The morbidity associated with vagotomy and pyloroplasty in patients with peptic ulcer disease is emphasized in Tables 7, 8 and 9. Ulcer disease was not present in any patient whose treatment was limited to repair of the hiatal hernia (Table 7). Tables 8 and 9 reveal that the total incidence of postoperative symptoms, the specific symptoms, and the duration of symptoms were almost identical when vagotomy and pyloroplasty were included regardless of the presence or absence of ulcer disease.

Eight of the 11 vagotomized patients with dumping had mild symptoms which were easily controlled by medical management. The remaining three patients had severe symptoms which were resistant to medical management (Table 10).

Some degree of obstruction occurred in a total of 78 patients (Table 11). However, if patients with preoperative obstruction due to a lower esophageal ring or stricture are deleted, only 42 patients (14%) had postoperative obstructive symptoms. In this group the majority of patients had mild symptoms which either subsided spontaneously or responded promptly to dilatation. Only 5 patients (2%) of the group without evidence of preoperative esophageal obstruction had severe symptoms which required repeated dilatation.

TABLE 2. *Comparison of Postoperative Symptoms to Operation*

Operation	Symptom				
	Symptomatic	Diarrhea	Cramps & Bloating	Nausea & Vomiting	Dumping
Repair only (134 Pts.)	57 (43%)	25 (19%)	51 (38%)	1 (1%)	0 (0%)
Repair & pyloromyotomy (18 Pts.)	5 (27%)	1 (6%)	4 (22%)	1 (6%)	0 (0%)
Repair + vagotomy & pyloroplasty (118 Pts.)	59 (50%)	44 (37%)	50 (42%)	20 (17%)	9 (8%)
Repair + vagotomy & resection (41 Pts.)	15 (37%)	10 (24%)	11 (27%)	0 (0%)	2 (5%)
Totals (311 Pts.)	136 (44%)	80 (26%)	116 (37%)	22 (7%)	11 (4%)

TABLE 3. *Comparison of Postoperative Symptoms to Operation*

Operation	Symptom				
	Symptomatic	Diarrhea	Cramps & Bloating	Nausea & Vomiting	Dumping
Repair without vagotomy (152 Pts.)	62 (41%)	26 (17%)	55 (36%)	2 (1%)	0 (0%)
Repair with vagotomy (159 Pts.)	74 (47%)	54 (34%)	61 (38%)	20 (13%)	11 (7%)
Total (311 Pts.)	136 (44%)	80 (26%)	116 (37%)	22 (7%)	11 (4%)

TABLE 4. *Duration of Postoperative Symptoms*

Operation	Symptomatic	< 3 Months	> 3 Months
Repair without vagotomy (152 Pts.)	62 (41%)	60 (40%)	2 (1%)
Repair with vagotomy (159 Pts.)	74 (47%)	33 (21%)	41 (26%)

TABLE 5. *Duration of Postoperative Symptoms*

Operation		< 3 Months	> 3 Months
Repair only	(134 Pts.)	55 (41%)	2 (2%)
Repair with pyloromyotomy	(18 Pts.)	5 (27%)	0 (0%)
Repair + vagotomy and pyloroplasty	(118 Pts.)	26 (22%)	33 (28%)
Repair + vagotomy and resection	(41 Pts.)	7 (17%)	8 (20%)
Totals	(311 Pts.)	93 (30%)	43 (14%)

Symptoms of gastroesophageal reflux and x-ray evidence of recurrent hiatal hernia are compared in patients with and without vagotomy in Table 12. Although the number of patients involved are small, the incidence of symptomatic and radiographic recurrence was higher in the vagotomized group. In Table 13, the recurrence rates are tabulated in relationship to the four operative combinations. Patients in whom vagotomy and pyloroplasty was included had approximately twice the recurrence rate of patients in whom treatment was limited to hiatal hernia repair. Twenty-seven patients had evidence of both symptomatic and radiographic recurrence of gastroesophageal reflux and hiatal hernia (Table 14). In this group, 16 patients had a repeat anti-reflux procedure and re-operation was recommended for an additional four patients. Vagotomy had been included in 13 of these 20 patients.

Discussion

This is a retrospective study of almost equal numbers of patients with symptomatic hiatal hernias managed by transabdominal anti-reflux procedures with or without adjunctive vagotomy. Morbid postoperative symptoms have been categorized as diarrhea, abdominal cramps and bloating, nausea and vomiting, and dumping. Significant postoperative symptoms occurred in 44% of the total series. However, the most striking feature is that only two (1%) of 152 patients in whom surgery was limited to the anti-reflux operation had postoperative symptoms lasting longer than three months; whereas, 41 (26%) of 159 patients with adjunctive vagotomy had persistant, incapacitating postoperative symptoms lasting longer than three months.

An analysis of these postoperative symptoms reveals that abdominal cramps and bloating occurred with an equal incidence with or without vagotomy (36%—without vagotomy; 38%—with vagotomy). This symptom complex is probably analogous to the "gas-bloat syndrome" described by Woodward.[3] Aerophagia manifested by belching occurs preoperatively in 92% of patients with gastroesophageal reflux[2] and continues postoperatively until the patient has made an adjustment to his newfounded freedom from the symptoms of gastroesophageal reflux. This symptom complex which occurred in this series where the Hill posterior gastropexy was used exclusively appears to be a function of the anti-reflux procedure rather than the adjunctive vagotomy.

A 20% incidence of longterm persistance of the "gas-bloat syndrome" is reported following the Nissen anti-reflux operation.[3] This syndrome is associated with left upper quadrant gastric distention with inability to belch. Following posterior gastropexy, no patient developed difficulty in belching. The ability of these pa-

TABLE 6. *Comparison of Postoperative Symptoms with Indication for Operation*

	Operation					
	Repair only		Repair + Vagotomy & Pyloroplasty		Repair + Vagotomy & Resection	
Indication	No. Pts.	Postop Symptoms	No. Pts.	Postop Symptoms	No. Pts.	Postop Symptoms
Uncontrolled esophagitis	58 (38%)	36 (62%)	56 (48%)	34 (61%)		
Symptomatic ring	5 (3%)	1 (20%)	13 (11%)	9 (69%)		
Obstruction-stricture	28 (19%)	6 (21%)	14 (12%)	9 (64%)		
Obstruction-incarcerated	14 (9%)	4 (29%)	5 (4%)	2 (40%)		
Acute hemorrhage	4 (3%)	1 (25%)	11 (9%)	1 (9%)		
Chronic anemia	5 (3%)	1 (20%)	4 (3%)	1 (25%)		
Gallbladder symptoms	38 (25%)	13 (34%)	3 (3%)	1 (33%)		
Peptic ulcer disease			12 (10%)	2 (17%)	41 (100%)	15 (37%)
Totals	152 (100%)	62 (41%)	118 (100%)	59 (50%)	41 (100%)	15 (37%)

TABLE 7. *Comparison of Postoperative Symptoms and Ulcer Disease*

Operation	No. Patients	Postop Symptoms
Repair only–ulcer present	0	
Repair + vagotomy and pyloroplasty–no ulcer	94	47 (50%)
Repair + vagotomy and pyloroplasty–ulcer present	24	12 (50%)
Repair + vagotomy and resection–no ulcer	0	
Repair + vagotomy and resection–ulcer present	41	15 (37%)

tients to belch appears to account for the transitory nature of these symptoms.

Diarrhea occurred in 35% of patients following vagotomy compared to 17% of patients without vagotomy. Nausea and vomiting, and dumping appeared to be associated with vagotomy rather than hiatal hernia repair as indicated by the significantly increased incidence in vagotomized patients. No patient in whom surgery was limited to an anti-reflux procedure developed symptoms of dumping.

The incidence of postoperative symptoms in patients operated upon for uncontrolled esophagitis was 62% when surgery was limited to the anti-reflux operation and 61% when vagotomy and phyloroplasty was included.

In contrast, the incidence of postoperative symptoms in patients with symptomatic lower esophageal ring and esophageal stricture treated by hiatal hernia repair alone manifested a significantly lower incidence of postoperative symptoms than the vagotomized group. An incidence of approximately 20% occurred without vagotomy compared to an incidence of approximately 65% with vagotomy.

The overall incidence of postoperative symptoms does not appear to be altered by the addition of vagotomy regardless of the presence or absence of ulcer disease. Even the incidence of specific symptoms were almost identical whether or not ulcer disease was present and persistant symptoms occurred equally in both groups (30%). It is of special interest that when vagotomy and pyloroplasty was included, dumping occurred only in those patients in whom *no* ulcer disease existed (Table 8).

TABLE 8. *Comparison of Postoperative Symptoms After Vagotomy and Pyloroplasty With and Without Ulcer Disease*

Symptom	No Ulcer (94 Pts.)	Ulcer Present (24 Pts.)
Symptomatic	47 (50%)	12 (50%)
Diarrhea	34 (36%)	10 (42%)
Cramps and bloating	39 (42%)	11 (46%)
Nausea and vomiting	17 (18%)	3 (13%)
Dumping	9 (10%)	0 (0%)

TABLE 9. *Comparison of Duration of Postoperative Symptoms After Vagotomy and Pyloroplasty With and Without Ulcer Disease*

Ulcer Disease	Symptomatic Patients	< 3 Months	> 3 Months
No ulcer (94 Pts.)	47 (50%)	21 (22%)	26 (28%)
Ulcer present (24 Pts.)	12 (50%)	5 (21%)	7 (29%)

Pyloromyotomy in combination with hiatal hernia repair was performed upon 18 patients. The indication for pyloromyotomy was the endoscopic finding of marked scarring of the pyloric channel sufficient to cause significant difficulty in passing the scope at the time of preoperative esophagogastroduodenoscopy. This procedure appeared to have no effect on the development of postoperative symptoms (Table 2).

Forty-two patients *without* preoperative symptoms had esophageal obstruction following operation. In patients with mild obstruction, the symptoms subsided spontaneously or responded promptly to dilatation. Although the number of patients with severe postoperative obstructive symptoms was small (5 patients), vagotomy and pyloroplasty had been performed upon each of these patients. Mechanical narrowing of the esophagogastric junction at the time of hiatal hernia repair is implicated as a major cause of postoperative esophageal obstruction when no obstruction existed preoperatively.

The incidence of recurrent gastroesophageal reflux symptoms and radiographic evidence of recurrent hiatal hernia was significantly greater in patients who had adjunctive vagotomy. This finding suggests that the addition of vagotomy does not provide additional protection against symptomatic or anatomic recurrence of hiatal hernia.

Hill[1] and Woodward[3] report that vagotomy does not improve the longterm results of hiatal hernia repair and is associated with significant longterm postoperative morbidity. Woodward[3] has indicated that the prolonged morbid postoperative symptoms associated with the Nissen procedure are severe enough to consider reserving this operation for recurrent or complicated gastroesophageal reflux problems. In contradistinction, the Hill posterior gastropexy used in this series, when

TABLE 10. *Incidence of Dumping Syndrome*

Operation		Total	Dumping: Mild	Dumping: Severe
Repair without vagotomy	(152 Pts.)	0 (0%)	0 (0%)	0
Vagotomy and pyloroplasty	(118 Pts.)	9 (8%)	7 (6%)	2 (2%)
Vagotomy and resection	(41 Pts.)	2 (5%)	1 (2%)	1 (2%)
Totals	(311 Pts.)	11 (4%)	8 (3%)	3 (1%)

TABLE 11. *Postoperative Esophageal Obstruction*

Operation		Mild Symptoms No.	Mild Symptoms Dilated	Severe Symptoms No.	Severe Symptoms Dilated
Repair only	(134 Pts.)	(23- 9*) 14 (10%)	(13- 7*) 6 (5%)	(4- 4*) 0 (0%)	(4- 4*) 0 (0%)
Repair with pyloromyotomy	(18 Pts.)	(3- 0*) 3 (17%)	(1- 0*) 1 (6%)	(1- 1*) 0 (0%)	(1- 1*) 0 (0%)
Vagotomy and pyloroplasty	(118 Pts.)	(25-12*) 13 (11%)	(12- 8*) 4 (3%)	(14- 9*) 5 (4%)	(14- 9*) 5 (4%)
Vagotomy and resection	(41 Pts.)	(7- 0*) 7 (17%)	(1- 0*) 1 (2%)	(1- 1*) 0 (0%)	(1- 1*) 1 (0%)
Totals	(311 Pts.)	(58-21*) 37 (12%)	(27-15*) 12 (4%)	(20-15*) 5 (2%)	(20-15*) 5 (2%)

* The number of patients with preop obstruction from ring or stricture were subtracted from the total number of patients for each operation.

TABLE 12. *Comparison of Symptomatic and X-Ray Recurrence*

Type of Operation	No.	Recurrence Symptomatic	Recurrence X-ray	Re-operation
Repair without vagotomy	152 (49%)	15 (10%)	13 (9%)	4 (3%)
Repair with vagotomy	159 (51%)	23 (15%)	22 (14%)	12 (8%)
Totals	311 (100%)	38 (12%)	35 (11%)	16 (5%)

TABLE 13. *Comparison of Symptomatic and X-ray Recurrences*

Type of Operation	No.	Recurrence Symptomatic	Recurrence X-ray	Re-operation
Repair only	134 (43%)	13 (10%)	9 (7%)	3 (2%)
Repair with pyloromyotomy	18 (6%)	2 (11%)	4 (22%)	1 (6%)
Repair + vagotomy and pyloroplasty	118 (38%)	21 (18%)	20 (17%)	10 (9%)
Repair + vagotomy and resection	41 (13%)	2 (5%)	2 (5%)	2 (5%)
Totals	311 (100%)	38 (12%)	35 (11%)	16 (5%)

TABLE 14. *Comparison of Symptomatic and X-ray Recurrences in Same Patient*

Operation	No.	Combined Symptomatic and X-ray Recurrence	Re-operation	Needs Operation
Repair only	134 (43%)	8 (6%)	3 (2%)	3 (2%)
Repair with pyloromyotomy	18 (6%)	1 (6%)	1 (6%)	
Repair + vagotomy & pyloroplasty	188 (38%)	16 (14%)	10 (9%)	1 (1%)
Repair + vagotomy & resection	41 (13%)	2 (5%)	2 (5%)	
Totals	311 (100%)	27 (9%)	16 (5%)	4 (1%)

performed *without* vagotomy, had only a 1% longterm complication rate and its use is recommended in the treatment of uncomplicated gastroesophageal reflux in addition to complicated and recurrent hiatal hernia problems.

This series clearly demonstrates that vagotomy significantly increases the incidence of longterm postoperative morbid symptoms and should be reserved for those patients in whom ulcer disease is documented when treating gastroesophageal reflux.

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DISCUSSION

DR. FRANCIS E. ROSATO (Norfolk, Virginia): I think Drs. Vansant and Baker are to be commended on the continuing and very critical review of their own most extensive experience with antireflux surgery. The initial advocacy of adjunctive vagotomy was a part of the so-called "balanced approach" to hiatus hernia reflux problems, wherein it was hoped that the correction of reflux and its pathology could be improved upon if the acid content of any residual reflux were to be minimized. In fact, there has appeared no significant literature to support the notion of increased acid secretion in patients with reflux problems, and over the years increasing attention has focused on the restoration of the lower esophageal sphincter pressure, and less and less attention has been focused on acid reduction.

I therefore emphatically restate Dr. Vansant's conclusion, and point out that acid reducing procedures in the course of correction of reflux problems should be reserved to those situations when such procedures would stand against the conventional criteria for their performance; namely, for acute peptic acid disease. Vagotomy does exact a price in the form of unpleasant symptoms. These symptoms do persist for some time, as we see from this review.

In our experience with the Hill posterior gastropexy, evaluated manometrically, we have been able to confirm the restoration of lower esophageal sphincter pressures to within 80% of the normal range. Equally important, we have shown a restoration toward a normal of the lower esophageal sphincter pressure in response to increases in intragastric pressure. In normal man, an increase in intragastric pressure produces an approximate twofold increase in lower esophageal sphincter pressure, thus guarding against regurgitation. The preoperative response in our own study group of patients was 0.5; that is, an increase in intragastric pressure produced only one half as much increase in lower esophageal sphincter pressure. After the performance of the Hill gastropexy, the ratio was restored to one-to-one, which is considerably improved over the preoperative status, and did correlate with the absence of reflux on x-ray.

Again, I would like to thank Drs. Vansant and Baker for this most informative presentation. When faced now with the age-old question, "What approach do I take to the repair of hiatus hernia?" I think the answer emphatically is: "Repair the lower esophageal sphincter, and thus restore its normal function. Reserve acid reducing procedures to those situations which would warrant them, irrespective of and independent of the reflux problem." Those situations, I believe, are relatively infrequent.

I would ask just one question of the presenters: How do they manage those patients who, after the performance of an antireflux procedure, show evidence by x-ray, of reflux but are free of any symptoms?—since I believe they have a few such patients in their presentation.

DR. OTTO C. BRANTIGAN (Baltimore): It is with reluctance that I speak about diarrhea to this astute audience. However, we have heard a lot about it this morning as related to vagotomy.

I have had the experience in the last six or seven years with about 350 selective gastric vagotomies for various causes and one does learn something about diarrhea.

The gastroenterologists state that, following pyloroplasty alone or pyloroplasty with vagotomy, there is a change in the bacterial flora in the terminal ileum. The flora can be altered by the use of tetracycline. I can verify this fact, that after selective gastric vagotomy, if the patient has diarrhea, the diarrhea will be promptly controlled by tetracycline, 250 mg, four times a day. The response is prompt and need not be continued for more than five days. If and when diarrhea reoccurs in a patient, it will respond to a repeat course of tetracycline. I suggest you try it.

Allow me to say a few words about truncal vagotomy. One of the reasons I could never accept truncal vagotomy in the treatment of many gastric problems was the complications that occurred with it. Yet when you read the literature, you believe that there is no difference between the two. There are differences. The persistent diarrhea that occurs after truncal vagotomy is one of the important differences. In my experience, zinc sulfate will control it.

It is with reluctance that I disagree with the authors on the ill effects of vagotomy as a part of the treatment of esophagitis with gastroesophageal reflux. Gastroesophageal reflux as the etiology in esophagitis is similar to gastric acidity, as the etiology in peptic ulcer of the stomach and duodenum. It is not the whole cause. Truncal vagotomy has many side effects that do not occur with selective gastric vagotomy. Vagotomy does change the character of the gastric contents that is refluxed. In my experience, selective gastric vagotomy has been useful as a part of the operation for reflux esophagitis.

DR. EDWARD R. WOODWARD (Gainesville, Florida): We began using vagotomy and drainage operation along with hiatal herniorrhaphy in 1954. It was only in retrospect, 15 years later, that we became aware 1) that the results in patients with and without vagotomy were no different in terms of control or recurrence of esophagitis, and 2) that the side effects were considerably increased by the additive surgery.

The only disagreement we have with the essayists is, first, dysphagia has been no more frequent with or without vagotomy in our experience, and it has been temporary in all cases. Secondly, we haven't noted any difference in either anatomical or clinical recurrence of hiatal hernia, with or without vagotomy.

It has been our experience that dumping has actually been about twice as frequent as diarrhea in complicating the patient who has had the added procedures.

In retrospect, I think it's clear that the esophageal mucosa is so tremendously sensitive to acid-pepsin that not only the interdigestive secretion of acid but the postprandial secretion of acid is *important* in its pathogenesis. Of course, this corresponds to the characteristic symptomatology of the patient, i.e. their symptoms are generally postprandial.

So we would state even more strongly than the essayists that vagal denervation of the stomach does not favorably effect reflux peptic esophagitis, that the amount of acid produced by the stomach is unimportant, as long as the surgeon accomplishes his objective of restoring the competence of the lower esophageal sphincter. We carefully preserve the vagi with our antireflux operations, unless the patient actually has a surgically significant duodenal ulcer.

DR. JOHN L. SAWYERS (Nashville): Dr. Vansant has conducted an extensive review of a large number of patients who have undergone hiatal hernia repair by the Hill technique. Approximately one half of the patients had truncal vagotomy, with three fourths of the vagotomy patients having pyloroplasty, and one fourth a gastric resection.

About 20 years ago, Dr. Jacob Berman, of Indianapolis, advocated the balanced operation for hiatal hernia. This consisted of a hiatal hernia repair by posterior crural suture, reconstruction of the angle of Hiss, truncal vagotomy, and pyloroplasty. Dr. Lynwood Herrington and I did several such operations in the late 1950's and early 1960's, and about ten years ago Dr. Ed Meads and I reported our results in 70 patients who had had a balanced procedure.

We thought that the results were better than those following hiatal hernia repair alone. This was before surgeons began to understand the lower esophageal sphincter mechanism, and before the effective antireflux procedures of Hill, Nissen, and Belsey. The balanced procedure of Berman accepted the fact that posterior crural repair did not always control reflux, and hoped that by lowering gastric acid secretion with vagotomy, and by doing a drainage procedure for rapid emptying of the stomach, patients would remain asymptomatic even if reflux still occurred.

As Dr. Vansant has pointed out, the accompanying vagotomy and drainage led to other problems, dumping and diarrhea. I do not think that the dumping symptoms are related to vagotomy, but occur because the integrity of the pylorus as a sphincter has been compromised. Truncal vagotomy, as we know, does alter bowel habits in a majority of patients, and may cause diarrhea in some.

We agree with Dr. Vansant that truncal vagotomy and the complementary procedures of pyloroplasty or resection are no longer indicated in patients requiring operation for gastroesophageal reflux. We prefer the Nissen fundoplication, rather than the Hill posterior gastropexy or the Belsey Mark IV operation, but all three operations are effective antireflux procedures.

In patients with active duodenal ulcer disease and gastroesophageal reflux, we would advocate parietal cell vagotomy with a fundoplication. Parietal cell vagotomy without drainage, as we heard from Dr. Paul Jordan this morning, is seldom accompanied by dumping or diarrhea. It is effective in healing duodenal ulcer. However, unless patients have a duodenal ulcer, or symptomatic gastric acid hypersecretion, there is probably no need for any type of vagotomy, but only an effective antireflux operation.

DR. JOHN W. BAKER (Closing discussion): Dr. Vansant and I appreciate the comments by all discussants, and I'd first like to address Dr. Rosato's question. He asked how we would manage the asymptomatic postoperative patient who is noted incidentally on postoperative GI series to have reflux of contrast material.

In general, we feel that the radiographic demonstration of gastroesophageal reflux is very significant, since it usually occurs only in patients with gross free reflux, and since the test is so apt to miss more subtle reflux. We also suspect, however, that reflux can be induced by manipulative means in many normal individuals. Therefore, our interpretation would depend upon the gymnastics that a particular radiologist performed. Should significant free reflux be demonstrated in the asymptomatic patient, we would be inclined to follow this patient carefully by clinical history and perhaps, re-endoscopy. We certainly would be concerned if we could find objective signs of continued marked esophagitis or stricture formation; however, in the absence of these findings, it would be very difficult to improve this asymptomatic patient's clinical situation.

Dr. Brantigan, we have not routinely used tetracycline for postoperative diarrhea, but will do so. I'm aware of your use of zinc sulfate, but, again, we have not used this, and look forward to doing so.

I enjoyed listening to Dr. Woodward's comments. I think after reviewing his paper presented here several years ago, that our paper further documents what he has previously said, and we agree with him wholeheartedly.

He mentioned that he had not had a higher incidence of dysphagia in patients who had had vagotomy in his series. I'm not sure that we have meaningful data on this, although we did have 42 patients who presented without preoperative dysphagia who postoperatively did have dysphagia. Only five patients, however, had persistent dysphagia, longer than three to six months, and all of those patients had vagotomy. I really am not sure how to interpret this.

I would also emphasize, as has Dr. Woodward, that we do indeed carefully preserve the vagus nerves in the performance of the Hill operation.

I'm very grateful to Dr. Sawyers for agreeing with us so much, and cannot take issue with him at all.

In summation, then, I would say that we feel this evidence further supports the evolved concept that gastroesophageal reflux and duodenal ulcer are two distinct clinical entities. We believe that this data is an indictment of vagotomy in the treatment of gastroesophageal reflux, on the basis of 1) its failure to prevent recurrence; and 2) on the basis of the long-term morbidity that we have seen with the use of vagotomy with antireflux procedures.

As a secondary emphasis from this material, we do endorse the transabdominal, posterior gastropexy for the management of gastroesophageal reflux—that is, the Hill repair—on the basis of its striking lack of long-term morbidity and a reasonable recurrence rate in our hands.

In addition to using this operation for straightforward gastroesophageal reflux, we are also using it for recurrent reflux following antireflux procedures which have been done either transthoracically or transabdominally, and are very pleased with those results. We are also using this in the management of dilatable esophageal strictures.

Total Duodenal Diversion for Treatment of Reflux Esophagitis Uncontrolled by Repeated Antireflux Procedures

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The operations of Nissen, Hill, and Belsey are adequate in controlling esophaegeal reflux in the majority of patients. In a small percentage however, objective and subjective evidence of esophagitis persists in spite of repeated operations to restore lower esophageal sphincter competency. These failures are then usually treated by operative procedures of great magnitude involving organ interposition. Repeated antireflux operations directed to the gastroesophageal area may in some instances result in impairment of blood supply with an increased risk of both esophageal and gastric fistulae. In the past many observers have felt that reflux esophagitis resulted solely from the effects of acid-pepsin secretions bathing the distal esophagus. Recently experimental and clinical data have indicated the importance of duodenal contents in the etiology and perpetuation of reflux esophagitis. During a recent two year period, 6 patients with persistent reflux esophagitis uncontrolled by repeated antireflux procedures have been seen on our service. These 6 patients, underwent 12 unsuccessful antireflux operations elsewhere. Three of the 6 patients had also been subjected to vagotomy-antrectomy for a coexisting duodenal ulcer. A marked lowering of gastric acidity took place but esophageal reflux and esophagitis persisted. These three patients were treated on our service by takedown of the Billroth I anastomosis, closure of the duodenal stump and diversion of the duodenal contents into a Roux-en-Y limb. Three other patients who had undergone unsuccessful antireflux procedures alone were subjected to antral resection, Roux-en-Y diversion and transthoracic vagotomy.

This simplified approach to the treatment of persistent esophageal reflux uncontrolled by repeated antireflux procedures has given satisfactory results. The operation should be considered when technical considerations preclude further surgical attempts to perform another effective antireflux operation. Total duodenal diversion should, however, not be considered as the primary operation for the patient suffering from reflux esophagitis. However, in circumstances discussed above this indirect approach appears preferable to major resectional procedures.

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THE OPERATIVE PROCEDURES of Nissen, Hill and Belsey are effective in controlling symptoms of esophageal reflux in 85% or more of cases.[11] In from 5 to 15% of patients continuation of reflux or objective evidence of esophagitis persists in spite of repeated direct attempts to restore lower esophageal sphincter competency. Such failures are then usually treated by either reversed tubular gastroplasty, jejunal or colonic interposition.

Repeated antireflux operations directed to the gastroesophageal junction may ultimately result in impairment of blood supply, tissue friability and anatomic distortion, with an increased risk of both esophageal and gastric fistulae and even gastroesophageal disconnection. Two such complications were recently referred to our service.

Formerly it was felt that reflux esophagitis resulted solely from the effects of acid-pepsin secretions.[1,3,20] Experimental investigators have now shown[10,16–18,43] the importance of bile and duodenal secretions as a major contributing factor. Also in the clinical setting, it has been demonstrated that duodenal contents alone may produce severe esophagitis with stricture formation.[25,31] Therefore, simple Roux-en-Y diversion has been advocated when direct operative approaches to control reflux have failed.

Clinical Material

During a recent two-year period, 6 patients with severe and persistent symptomatic reflux esophagitis uncontrolled by previous antireflux operations were treated

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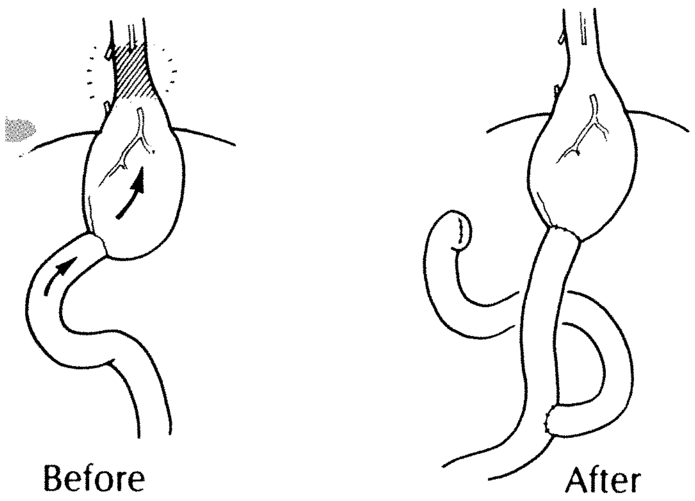

FIG. 1. Three patients experienced esophagitis secondary to persistent reflux and also had previously undergone truncal vagotomy-antrectomy for duodenal ulcer. Each was treated by Roux-en-Y diversion.

on our service. There were 4 men in the group and 2 women whose ages range from 33 to 66 years. Two of the 6 patients had each undergone, elsewhere, a single unsuccessful attempt at correction of reflux. Two patients had each been subjected to two unsuccessful antireflex procedures and two patients had each undergone three operative attempts for control of reflux with continuation of symptoms.

When seen on our service distal esophageal reflux with esophagitis was documented by endoscopy with biopsy in each of the 6 patients. An associated sliding esophageal hiatal hernia had originally been demonstrated radiographically in each patient. Lower esophageal sphincter pressure was recorded in two patients, and each showed a marked reduction in sphincter competency. Three of the 6 patients originally had a duodenal ulcer in addition to esophageal reflux and at the time of the antireflux procedure also underwent truncal vagotomy with distal gastric resection and a Billroth I reconstruction.

After thorough preoperative evaluation the three patients with prior vagotomy-resection were treated by Roux-en-Y diversion (Fig. 1). The three patients who had undergone only previous antireflux procedures were subjected to distal gastric resection with Roux-en-Y diversion. Truncal vagotomy was, likewise, added and was performed by the transthoracic route as the anatomical distortions about the gastroesophageal junction and the possibility of operative injury to structures in this area precluded a transabdominal vagotomy (Fig. 2).

Case Reports

Case 1: A 33-year-old man was admitted 1-22-74 with the complaint of epigastric and substernal pain along with regurgitation. Two years prior he had undergone truncal vagotomy-resection with a Billroth I reconstruction for a benign gastric ulcer. In addition, a sliding esophageal hiatal hernia was also corrected. Following operation symptoms of ulcer disease were controlled but the patient continued to experience substernal burning and regurgitation.

One year before admission the patient was subjected to another laparotomy, and an antireflux procedure incorporating modifications of both the Hill and Nissen techniques were performed. Postoperatively no improvement took place and a 20-pound weight loss later occurred. The patient continued to experience regurgitation daily.

Upon admission to St. Thomas Hospital endoscopy revealed moderately severe distal esophagitis without ulcerations. A moderate degree of gastritis was also present and the gastroduodenal anastomosis appeared normal.

At operation on 1-28-74 the abdomen was re-entered through the previous mid-line scar. The adhesions in the left upper abdominal quadrant were so extensive that they precluded any attempt at performing another antireflux procedure. Therefore, it was elected to divert the total duodenal content into a Roux-en-Y limb. The postoperative course was excellent and the patient was discharged on the 12th postoperative day.

Followup gastrointestinal series showed the gastroenterostomy to function properly and endoscopy reveals no evidence of esophagitis. The patient, however, continues to note transient upper abdominal fullness after meals and intermittent mild abdominal discomfort. In spite of these symptoms he has received considerable benefit from the remedial operation. The followup extends to almost two years (Fig. 3).

Case 2: A 60-year-old man was admitted 8-1-74 with the complaint of substernal discomfort, epigastric fullness and frequent regurgitation of food. Six months prior he had undergone, elsewhere, a truncal vagotomy-antrectomy with a Billroth I reconstruction for duodenal ulcer along with a crural sling repair of a sliding esophageal hiatus hernia.

Following discharge, symptoms of severe substernal distress and regurgitation with frequent aspirations necessitated treatments in the out patient clinic. During the following months symptoms progressed in severity and a 20-pound weight loss took place.

Upon admission to our institution the patient was in moderate respiratory distress and a marked hypochromic anemia was found. Fiberoptic bronchoscopy revealed a tremendous amount of purulent bronchial secretions but no evidence of neoplasm was present. Chest x-rays showed evidence of pulmonary vascular congestion and aspiration pneumonitis.

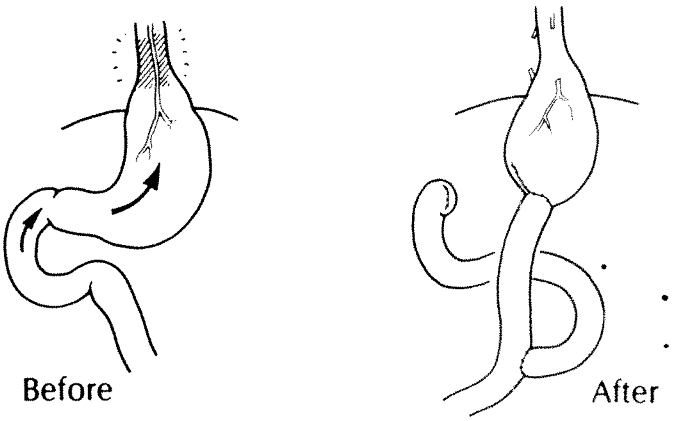

FIG. 2. Three patients with persistent esophageal reflux after failure of antireflux procedures were treated by antrectomy with Roux-en-Y diversion and transthoracic vagotomy.

Fiberoptic endoscopy revealed marked inflammation with erosions, ulcerations and exudation involving the distal one-half of the esophagus. A mild distal esophageal stricture was present along with areas of gastritis throughout the gastric remnant. Multiple biopsies of both the esophageal and gastric mucosa showed no evidence of malignancy. A gastrointestinal barium study resulted in prompt aspiration of the media into the bronchial tree and a barium bronchogram of the right lower lobe segmental bronchi was obtained (Fig. 4). The study was immediately terminated and the tracheobronchial tree aspirated.

After approximately one month of intensive pulmonary treatment it was apparent that operation was necessary to control the severe and persistent esophageal reflux. The abdomen was re-entered through the long mid-line scar. There was extensive fibrosis and scarring about the gastroesophageal junction. Normal anatomic landmarks were distorted and it was felt that further dissection in this area would certainly compromise the already endangered blood supply. Therefore, it was decided to divert the total duodenal content from the esophagus. The gastroduodenal anastomosis was dismantled and a Roux-en-Y diversion performed 60 cm distal to the gastroenteric stoma.

A repeat endoscopic examination on the 19th postoperative day revealed the esophagus to be normal. Except for a minor cardiac problem the remainder of the hospitalization was unremarkable. During the postoperative followup, now extending to 16 months, the patient has continued to do well. His pulmonary status has undergone marked improvement and he has had no further episodes of aspiration pneumonitis.

Case 3: A 53-year-old woman was admitted to the hospital on 6-1-74 with the complaints of severe upper abdominal fullness after meals and frequent regurgitation of food. Past history revealed that 5 years prior she had undergone, elsewhere, transabdominal repair of a sliding esophageal hiatus hernia. Symptoms were not relieved and approximately one year later a transthoracic Belsey antireflux procedure was performed. Symptoms, however, persisted and two years later abdominal re-exploration was again undertaken and a Nissen fundoplication was done along with splenectomy. No relief was obtained and a rigid medical program was again instituted without benefit.

At the present admission endoscopy showed the presence of a hiatus hernia with demonstrable reflux. A grade two distal esophagitis was present but no ulcerations or evidence of malignancy were noted.

At laparotomy dense adhesions were encountered in the left upper abdomen. Technically, it was impossible to dissect the distorted anatomy about the gastroesophageal junction. Therefore, it was elected to remove the distal 50% of the stomach, close the duodenal stump, and perform a Roux-en-Y diversion. On the 10th postoperative day a transthoracic vagotomy was performed.

The patient has now been followed for 18 months and has been completely relieved of symptoms of abdominal fullness and regurgitation. Esophagoscopy and gastroscopy studies during the followup reveal no evidence of reflux and the distal esophagus and gastric remnant appears normal.

Case 4: A 66-year-old man was admitted 3-8-74 with burning epigastric pain, epigastric fullness and substernal distress and regurgitation. In 1972 he had undergone, elsewhere, a crural sling repair of a large sliding esophageal hiatus hernia associated with reflux. No relief was obtained, and several months later a gastrointestinal barium study

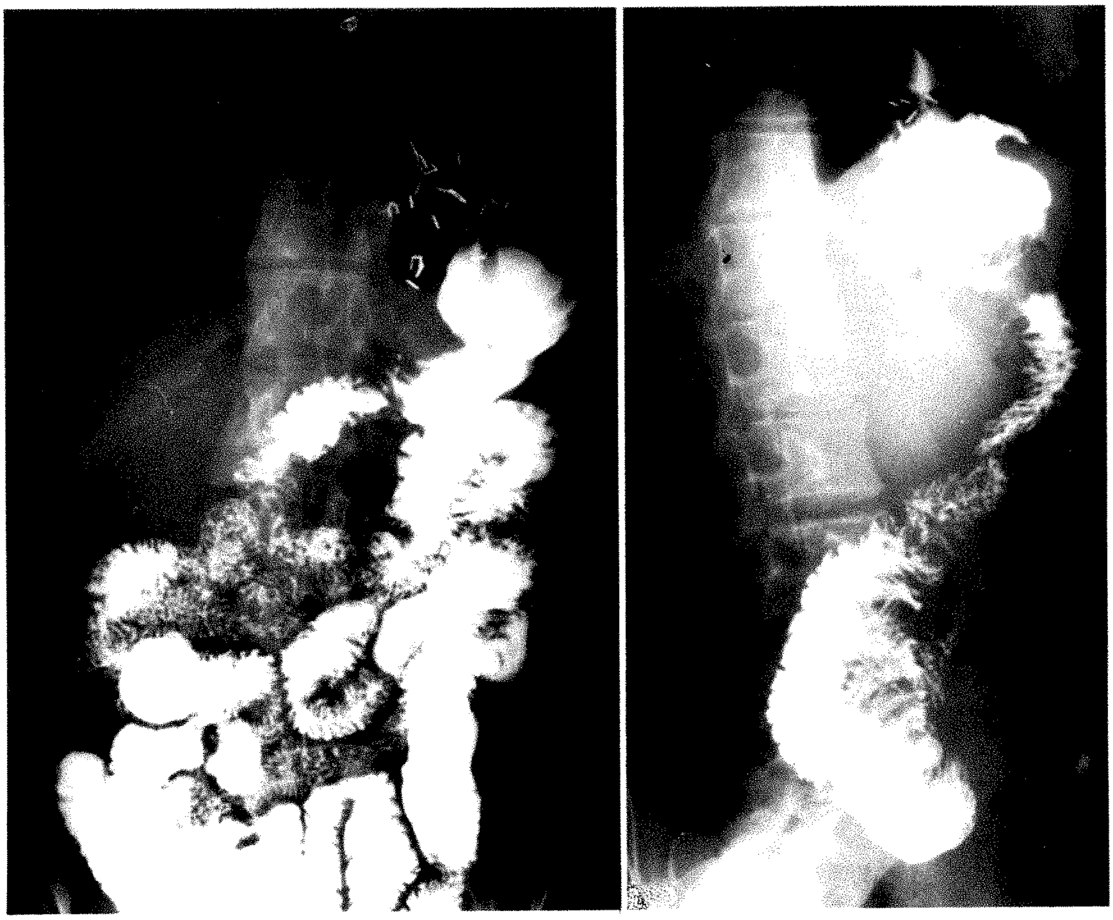

FIG. 3. (Case 1) (Left) upper gastrointestinal barium study in a patient with persistent esophageal reflux and a recurrent hiatus hernia who had also undergone truncal vagotomy-antrectomy with a Billroth I reconstruction for duodenal ulcer. (Right) Postoperative study after correction of persistent reflux esophagitis in this achlorhydric patient by takedown of the Billroth I anastomosis, closure of the duodenal stump and Roux-en-Y diversion.

revealed the hernia still present. In August of 1973 he underwent a Nissen fundoplication in an attempt to control reflux. The operative procedure again provided no relief of symptoms.

When seen at our institution of gastrointestinal series demonstrated a fairly large recurrent sliding esophageal hiatal hernia with considerable esophageal reflux. Endoscopy showed a moderate degree of esophagitis with associated gastritis, and the duodenal bulb was normal. Biopsies showed no sign of malignancy. Resting lower esophageal sphincter pressure was 6 mm Hg.

At re-operation the mid-line abdominal scar was excised and extremely dense adhesions were encountered in the left upper abdominal quadrant. The dissection about the gastroesophageal junction was extremely tedious and difficult but the Nissen fundoplication appeared intact. A portion of the plication lay in the posterior mediastinum and the vagus nerves were incorporated within the wrap-around. It was our opinion that to dismantle the fundoplication and to attempt to reconstruct it in a more efficient manner would be extremely difficult and perhaps hazardous. Therefore, treatment consisted of an estimated 60% distal gastrectomy with reconstruction using a gastrojejunostomy with Roux-en-Y diversion. Since vagotomy could not be technically accomplished through the abdominal approach, a transthoracic vagotomy was carried out 10 days later.

Since discharge he has been relieved of all symptoms and endoscopy shows the esophagus to be entirely normal. The followup period extends to 9 months. Postoperative upper gastrointestinal study shows a normal gastric remnant with no evidence of delayed evacuation. The hiatus hernia is again visualized (Fig. 5).

Case 5: A 40-year-old woman was admitted September 1, 1974 with a 10-year history of epigastric discomfort and substernal burning distress. She had been diagnosed as having an active duodenal ulcer and a sliding esophageal hiatus hernia with esophageal reflux. In 1971 she underwent, elsewhere, a truncal vagotomy-antrectomy with a Billroth I reconstruction and a modified Allison repair of the hiatus hernia. Symptoms of ulcer were well controlled but the patient continued to complain of substernal discomfort along with regurgitation. Repeat barium studies of the upper gastrointestinal tract showed a recurrence of the hiatus hernia with evidence of reflux but no anastomotic ulcer was detected. The patient underwent another attempt at transabdominal correction of the esophageal reflux. Again the result was unsuccessful and in 1973 a third antireflux procedure was attempted but objective and subjective evidence of reflux persisted.

When seen on our service gastrointestinal series revealed evidence of a moderate size sliding esophageal hiatal hernia with demonstrable reflux. Endoscopy showed severe distal esophagitis but no stricture was present. A moderate degree of superficial gastritis was also noted. Acid secretory studies revealed no titratable basal acid and the peak acid output was 0.8 meq/hr.

At re-operation through the previous mid-line abdominal scar in intense amount of scarring was found about the gastroesophageal junction, and it was felt that further attempt at constructing an effective antireflux procedure would be fraught with technical difficulties. Therefore, the Billroth I reconstruction was taken down and Roux-en-Y diversion performed.

Endoscopic examination 6 months following discharge revealed no evidence of esophagitis. She has continued to do well over a 15 months followup and experiences no dietary restrictions.

Case 6: A 46-year-old man was first seen in October 1974 with a 3-year history of retrosternal burning pain and upper abdominal discomfort made worse by food intake. He had been diagnosed elsewhere has having an esophageal hiatus hernia.

A gastrointestinal series revealed a sliding esophageal hiatal hernia with considerable reflux of barium into the distal esophagus. On endoscopy linear ulcerations and erosions were present in the distal esophagus and a small hiatus hernia was visualized. The stomach and duodenum appeared normal.

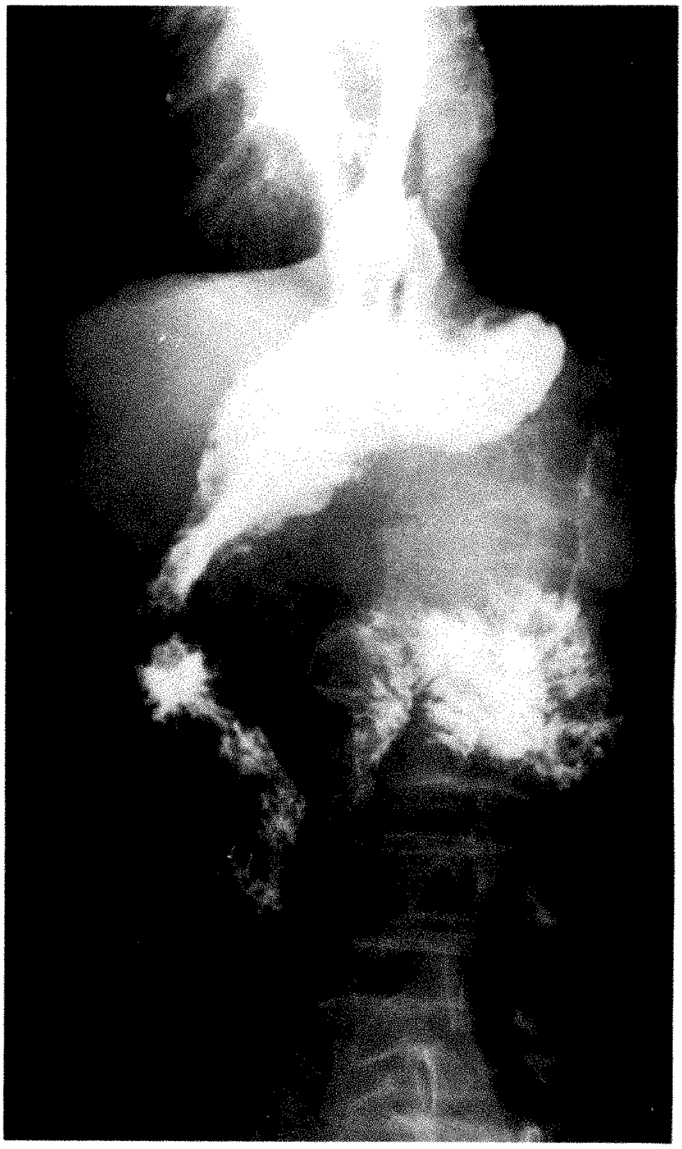

FIG. 4. (Case 2) Upper gastrointestinal barium study of a patient with persistent esophageal reflux and severe esophagitis. The recurrent hernia is demonstrated and the patient has had the gastric antrum removed with a Billroth I reconstruction. Note the barium bronchogram resulting from aspiration of the contrast media.

Operation was advised and on 10-10-74 the abdomen was opened through a transverse supraumbilical incision. Positive findings were limited to the presence of a sliding esophageal hiatal hernia which was corrected by reduction and approximation of the crural sling posterior to the esophagus in combination with a Nissen fundoplication.

The patient did well for approximately two months but then developed epigastric pain and severe discomfort in the mid thoracic area posteriorly. The pain was exaggerated by eating but no dysphasia was noted. A 10-pound weight loss took place over the next several months. Endoscopy now showed a large shallow ulceration which measured 1½ × 1 cm and was located 28 cm from the incisor teeth. No evidence of a stricture was demonstrated. The stomach and duodenum again appeared normal. Multiple biopsies of the ulcer and the esophageal mucosa just distal to the ulcer revealed the presence of a benign superficial *gastric ulcer* with surrounding inflammation.

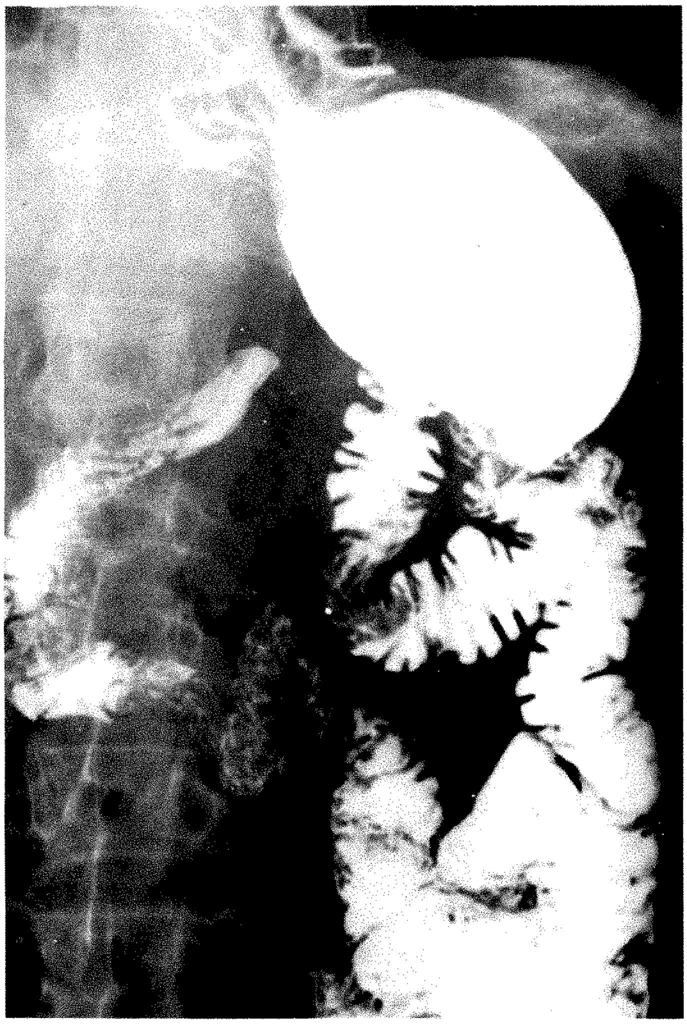

FIG. 5. (Case 4) Postoperative barium examination following antrectomy with Roux-en-Y diversion and transthoracic vagotomy. Note the hiatus hernia persists.

Glandular elements were demonstrated and columnar epithelium was present in the distal esophagus beyond the ulcer. No parietal cells were identified in the ulcer or in the columnar epithelium distal to the ulcer. These findings were compatable with the diagnosis of a Barrett ulcer[2,4–6] of the esophagus. Vigorous treatment with diet and antacids during the next several months failed to relieve the pain. Also repeat endoscopy showed the ulcer to be essentially unchanged. It was felt at this time that further conservative treatment was inadvisable and surgical intervention was indicated. Several surgical procedures were considered such as resection of the lower two-thirds of the esophagus with colonic interposition, attempt at another Nissen fundoplication or even posterior gastropexy in hopes of restoring (LES) competency, or the use of Roux-en-Y diversion.

At re-exploration an intense chronic inflammatory reaction was found about the gastroesophageal junction with marked distortion of anatomical landmarks. The fundoplication had not disrupted but further surgery in this area was deemed inadvisable. Therefore, it was decided to perform an estimated 50% distal gastric resection with Roux-en-Y reconstruction. A transabdominal vagotomy could not be accomplished at the vagus nerves were encased within the gastric-fundic wrap-around. Vagotomy was done via the left transthoracic approach.

Endoscopic examination on the 11th postoperative day revealed the Barrett ulcer to have completely healed and the esophagus was free of inflammation and ulceration. Barium study revealed the gastric pouch to be normal. No reflux could be demonstrated and the gastroenteric stoma emptied adequately.

Since discharge the patient has had no further epigastric or back discomfort. He is able to eat three meals daily and during the following months has regained his lost weight. A recent endoscopic examination 6 months after operation reveals the esophagus free of ulceration and inflammation and no reflux of gastric remnant contents into the esophagus can be demonstrated. Columnar epithelium is again demonstrated lining the distal esophagus and parietal cells can now be identified (Fig. 6).

Results

The patients have now been followed from a minimum of 6 months up to 23 months. Four patients have been observed in excess of one year. Five of the 6 have obtained an excellent clinical result and repeated endoscopies show no evidence of esophagitis. In one patient (Case 1) subjective improvement has been noted but he still experiences epigastric fullness at times. Endoscopic examination, however, shows no evidence of esophagitis. None of the 6 patients experienced vasomotor or gastrointestinal symptoms of the dumping syndrome.

Discussion

Up until recent years it was generally taught that acid-pepsin secretions were the sole culprits responsible for inflammatory changes in the distal esophagus secondary to esophageal reflux. Wangensteen and Leven[39] were among the first to report several patients with duodenal and gastric ulcers, who in addition experienced reflux esophagitis, the latter manifestations being improved following subtotal gastric resection. In latter studies both Ferguson[16] and Cross[9,10] working in Wangensteen's laboratory clearly demonstrated the importance of bile and pancreatic juice in the production of esophageal erosions and showed that total excision of the acid secreting portion of the stomach did not prevent experimentally induced esophagitis. Kelly and Wangensteen[26] and also Helsingen of Oslo[21,22] in both experimental and clinical settings showed that reflux of duodenal contents into the distal esophagus after total gastrectomy with esophagoduodenostomy or esophagojejunostomy resulted in severe inflammatory changes.

Several clinical reports have cited reflux esophagitis or esophagitis with stricture as a complication of subtotal gastric resection performed for gastroduodenal ulcer disease.[8,28,44] Such patients had little or no acidity in their gastric juice. Cenni[7] described 3 patients with severe esophagitis following a Polya type Gastrectomy, each

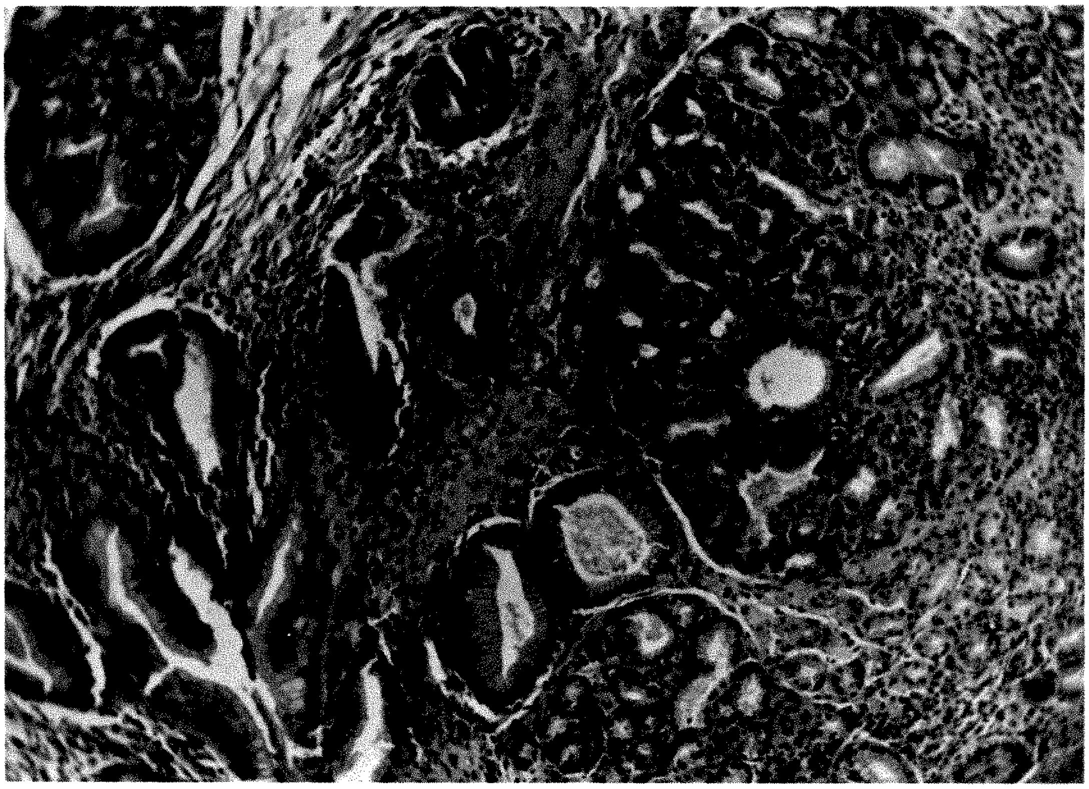

FIG. 6. (Case 6) Postoperative endoscopic biopsy of the esophageal mucosa reveals the presence of columnar epithelium lining the distal one-hald of the esophagus. No evidence of ulceration is now noted and parietal cells can not be identified throughout the columnar mucosal columns.

being relieved of symptoms after a Rous-en-Y diversion. Himal[24] reported 5 patients with marked esophagitis following gastric resection, each of whom was cured by the use of a duodenal diversion procedure.

With few exceptions[12,34,35,42] the vast amount of current experimental literature suggests that duodenal contents are injurious to the esophageal mucosa. In sophisticated reflux studies using the rat, Lambert[27] produced a 79% incidence of documented esophagitis using pancreatic juice alone and a 28% incidence when reflux was limited to bile alone. He felt that the presence of bile potentiated the destructive action of pancreatic juice on the esophageal mucosa. Moffat,[29] using isolated biliary conduits, showed that canine bile was capable of producing various degrees of erosive esophagitis.

In reflux experiments using the Rhesus money, a primate with a gastric secretory apparatus and gastric anatomical structure similar to man, Gillison and Nyhus[17,18] were able to show that bile contamination of the gastric juice produced esophagitis of varying grades. In the presence of the bile contamination procedure (cholecystogastrostomy) the animals then received daily injections of Depot Histamine but the degree of esophagitis was observed not to worsen. Of extreme interest was the observation that those animals subjected to pylorectomy and Roux-en-Y diversion failed to develop esophagitis when later subjected to a reflux operation. The animals were noted, however, to reflux acid-pepsin chyme which produced no inflammatory insult to the esophageal mucosa. Studies in the human by Gillison[19] have shown that the symptoms of heartburn are associated with reflux of duodenal contents into the stomach and esophagus.

Holt and Large[25] were perhaps the first to use Roux-en-Y diversion for the treatment of reflux esophagitis and esophageal stricture. In a clinical experiment they observed a patient develop reflux esophagitis following the Grondahl-Heyowsky operation performed for achalasia. A subsequent distal gastric resection of the Billroth II type proved ineffective as the patient's symptoms and the endoscopic esophageal changes persisted. Analysis of aspirations from the inflamed esophagus revealed fluid high in bile and amylase content. Diversion of the duodenal contents into a Roux-en-Y limb along with vagotomy to protect against recurrent ulceration proved effective in correcting the esophageal inflammatory changes. These same authors reported 10 cases of reflux esophageal stricture treated by distal gastric resection with Roux-en-Y diversion. In 4 of the 10 patients the stricture necessitated resection. The early followup results were excellent. More recently, Weaver[40] has reported an 8 to 17-year followup on the 10 patients and no incidence of recurrent esophagitis or stricture has taken place. The reflux of gastric contents continues as demonstrated by endoscopy and fluoroscopy, but without apparent symptoms or esophageal mucosal changes. Recently Royston and Spencer[36] reported 8 patients with severe esophageal stricture secondary to reflux who were treated by dilatation of the stricture, antrectomy and Roux-en-Y diversion. Results were excellent over a followup period ranging from 11 to 20 months.[38,41] In 1956 Ellis[13-15] described an operation for reflux esophagitis and stricture which consisted of a limited resection of the diseased esophagus, truncal vagotomy, and antral resection with gastroduodenostomy. The early results were reviewed as promising. In a subsequent report 7 years later, Payne and Ellis[31] reviewed a total of 34 patients and showed that the failure rate had increased from 4% in the early postoperative study to 21%. The failures were considered to be the result of reflux duodenal secretions. As a result of this experience Payne later reported satisfactory early results using either Roux-en-Y diversion or a Henley loop procedure. Currently he has had a large and successful experience using vagotomy-antrectomy and Roux-en-Y diversion in the treatment of this complicated problem.[30,33]

Smith and Payne[37] have also observed severe reflux esophagitis as a complication of distal esophagectomy and proximal gastrectomy with esophagoantrostromy done for carcinoma of the esophagogastric junction. The reflux was corrected by Roux-en-Y diversion. Hill[23] has, likewise, carried out a similar remedial operation in a patient who developed disabling reflux esophagitis after proximal gastrectomy and distal esophagectomy with esophagoantrostomy done for sarcoma of the proximal stomach.

It is our current opinion that the indirect operative approach of Roux-en-Y diversion for the treatment of persistent esophageal reflux uncontrolled by repeated antireflux procedures is indicated in selected cases. It should be given serious consideration when a severe chronic inflammatory process is found present in the left upper abdominal quadrant, when normal anatomical landmarks are distorted, and when there is fear that the vascular supply to the area may be compromised. No doubt the most important component to the operation for the correction of persistent esophagitis is diversion of the total duodenal content. Distal gastric resection and vagotomy are, however, mandatory to prevent the development of a marginal ulcer.

It should be emphasized that the procedure is indeed selective and is indicated only when previous antireflux procedures fail. The operation should not be used as the initial procedure for the patient suffering from reflux esophagitis with or without hiatus hernia. However, in the circumstances under discussion this rather simplified approach seems preferable to major resectional procedures.

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Discussion

Dr. Thomas Bombeck (Chicago): I am just coming from having scheduled my seventh of Dr. Herrington's diversion operations, and this one for exactly the same sort of problems as he described in presenting this paper. I read the paper just before this presentation with considerable interest. I agree with everything except for the last paragraph where he said that it should be used only as a secondary procedure, and only in selected patients. My question is: Why?

I ask this question because it has now been well demonstrated in numbers of series on alkaline gastritis and alkaline esophagitis that duodenal content really belongs in the duodenum. It doesn't belong in the stomach, and it doesn't belong in the esophagus.

Now, in our own studies, to which he has alluded, both in his presentation and in the manuscript, we have demonstrated an 85% incidence of bile salt reflux in the more severe degrees of esophagitis. We divide esophagitis into four degrees. The two worst ones, numbered 3 and 4, are very, very severe reflux esophagitis, with ulceration and/or stricture, or frank Bareth ulcer. In those patients you can aspirate bile sale from the esophagus 85% of the time.

Furthermore, increased gastroscopy—increased used of that modality, especially by surgeons—has demonstrated an ever-increasing incidence of biliary gastritis. Because of those two things, I suggest that this operation, as initially described by Dr. Herrington for alkaline gastritis, and now for alkaline esophagitis, is a valuable addition to the armamentarium of the surgical gastroenterologist, where the patient in whose disease complex reflux of duodenal content plays a part, whether primary or secondary. This should be the indication for its use, not failure of something else.

I would like Dr. Herrington's comments on that particular point.

Dr. George L. Jordan, Jr. (Houston): Dr. Herrington, as usual, has brought us an interesting and provocative paper. As he has pointed out, surgeons have been interested in acid-pepsin digestion for years, and have tested the effect of acid and pepsin in virtually every part of the gastrointestinal tract. But it's been relatively recent, interestingly enough, that interest has developed in the digestive capacity of alkaline secretions.

I think it's unfortunate that the term "bile gastritis" or "reflux alkaline gastritis" is the term that's applied, because what really refluxes, of course, as Dr. Herrington points out is his paper more specifically, is duodenal content.

We're all familiar with the action of duodenal content on the skin around a duodenal fistula, and at the other end of the gastrointestinal tract, around an ileostomy. This is activated pancreatic juice as well as bile, and this is a highly digestive solution. Thus it is not too surprising that when it gets into the esophagus, it will really cause trouble.

On the other hand, I think most of us are lulled into a sense of security about the esophagus, simply by watching what our friends ingest by mouth. You know, you'll drink coffee that you wouldn't dare put your hand in, and nothing much happens. In our part of the country people eat Jalapeno peppers, which makes them breathe flames, and nothing much happens. And I have patients who drink three quarts of 100 proof liquor per day, a substance that can coagulate some protein, but not that of the esophagus.

Thus we think the esophagus is almost indestructible, when in actuality it's not. It's really quite sensitive to digestion by duodenal contents.

Thus I consider this a very rational and decidedly simpler procedure than many that we have used to control the difficulties which have been described. I happen to agree with Dr. Herrington, however, that this should be used only in selected patients, and in patients with specific problems.

I would like to point out that most of us aren't going to have much trouble with this, because if Dr. Herrington's only treated six of these, when he's performed 3500 gastrectomies, we won't see many of these problems very often.

Dr. J. Lynwood Herrington, Jr. (Closing discussion): Dr. Bombeck, I have been quite pleased with the results that we and others have obtained using the Nissen fundoplication as the primary operation to control esophageal reflux with or without hiatus hernia and we have only used the Roux-en-Y reconstruction in the problem cases that I have just presented. I think that if the Roux-en-Y reconstruction was used as the primary operation to control reflux we would certainly have a number of patients develop a dumping syndrome, post vagotomy diarrhea, and other long term sequelae. However, I do think that for the treatment of a primary duodenal ulcer if one cannot perform a Billroth I reconstruction after vagotomy-antrectomy I would heartily endorse reconstruction using the Roux-en-Y method in preference to a Billroth II type of reconstruction. In our experience we have had a sizeable number of complications using the Billroth II type reconstruction and this has been the experience of others. Particularly do I have reference to the development of reflux gastritis following a Billroth II reconstruction and this may require remedial surgery with conversion to a Roux-en-Y reconstruction as a primary operation for duodenal ulcer disease in preference to the Billroth II method.

When one operates upon the gastroesophageal junction for the second, third or fourth time to control persistent reflux I think that in certain instances one may inflict injury to this area with severe complications following. Now the literature contains only a scattering number of case reports depicting injury to the gastroesophageal junction following attempts to control persistent reflux, but no doubt these injuries are not by any means rare and no doubt many of them are never reported in the surgical literature.

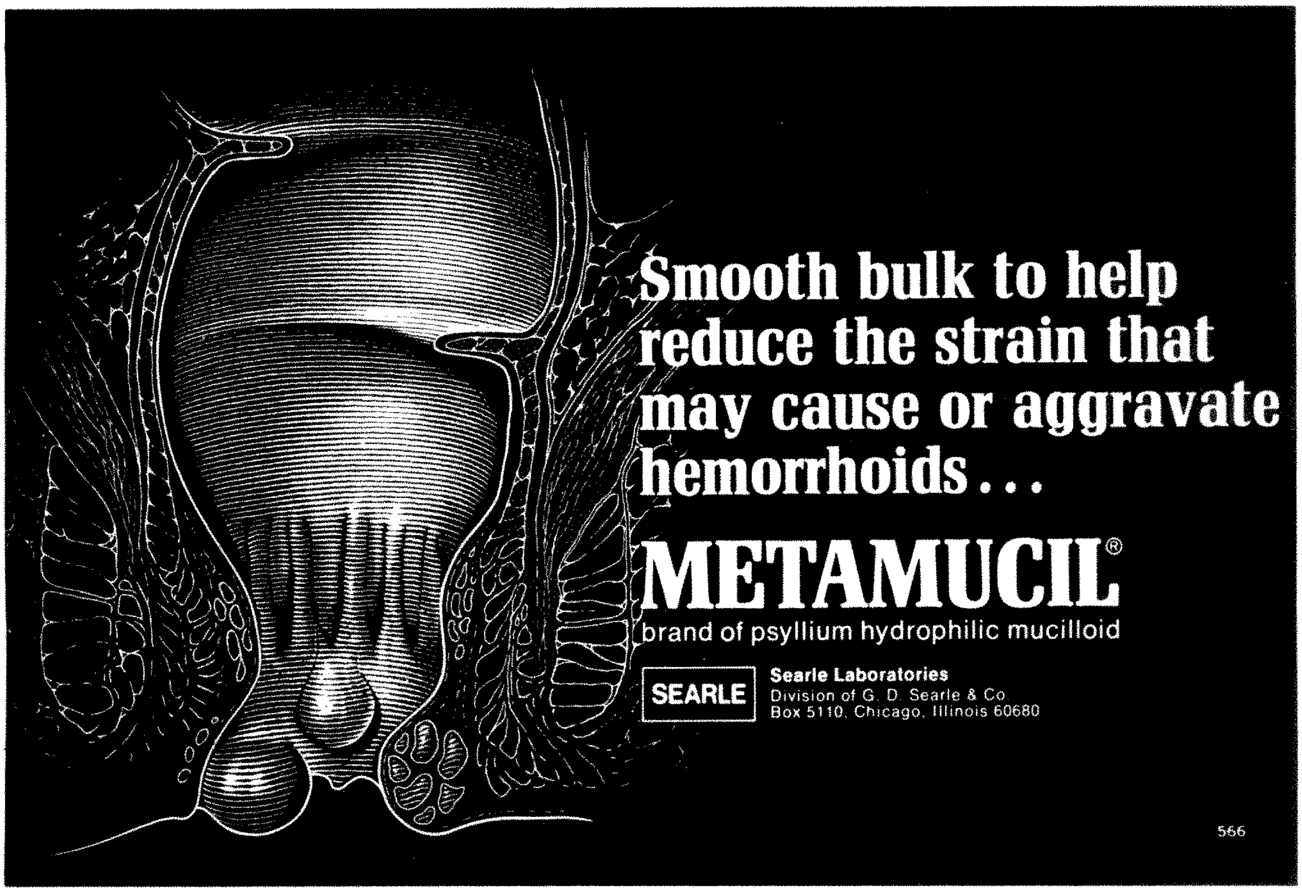
(Slide) Within the past two years we have encountered two patients referred to us with severe injury to the gastroesophageal junction. This slide shows a patient who was operated upon elsewhere three different times, once through the left chest and twice through the abdomen in an attempt to control persistent esophageal reflux. The barium study depicts that the fourth operation about the gastroesophageal junction resulted in an esophagogastrocutaneous fistula.

(Slide) This is the same patient several days later who on repeated gastrointestinal study now has a gastric fistula which has penetrated into the descending colon. This patient, needless to say, was quite ill and extremely septic. She was treated with multiple decompressions and multiple drainage procedures and after several months in the intensive care unit she did finally recover.

(Slide) This is a gastrointestinal series of another patient who had five unsuccessful attempts to control esophageal reflux. As you see here, the patient again has an esophagogastrocutaneous fistula. The patient was treated with extensive drainage and supportive measures but developed a down-hill course.

(Slide) This is a chest x-ray sometime later on the same patient and here you see a widened mediastinum with air present in the pericardium. The gastric fistula had penetrated into the pericardial sac and the patient expired.

I distinctly feel that had these patients been treated with a Roux-en-Y diversion rather than a further attempt to free up the gastroesophageal junction in an attempt to control reflux that both patients would have, no doubt, survived and would have been cured of their problem.



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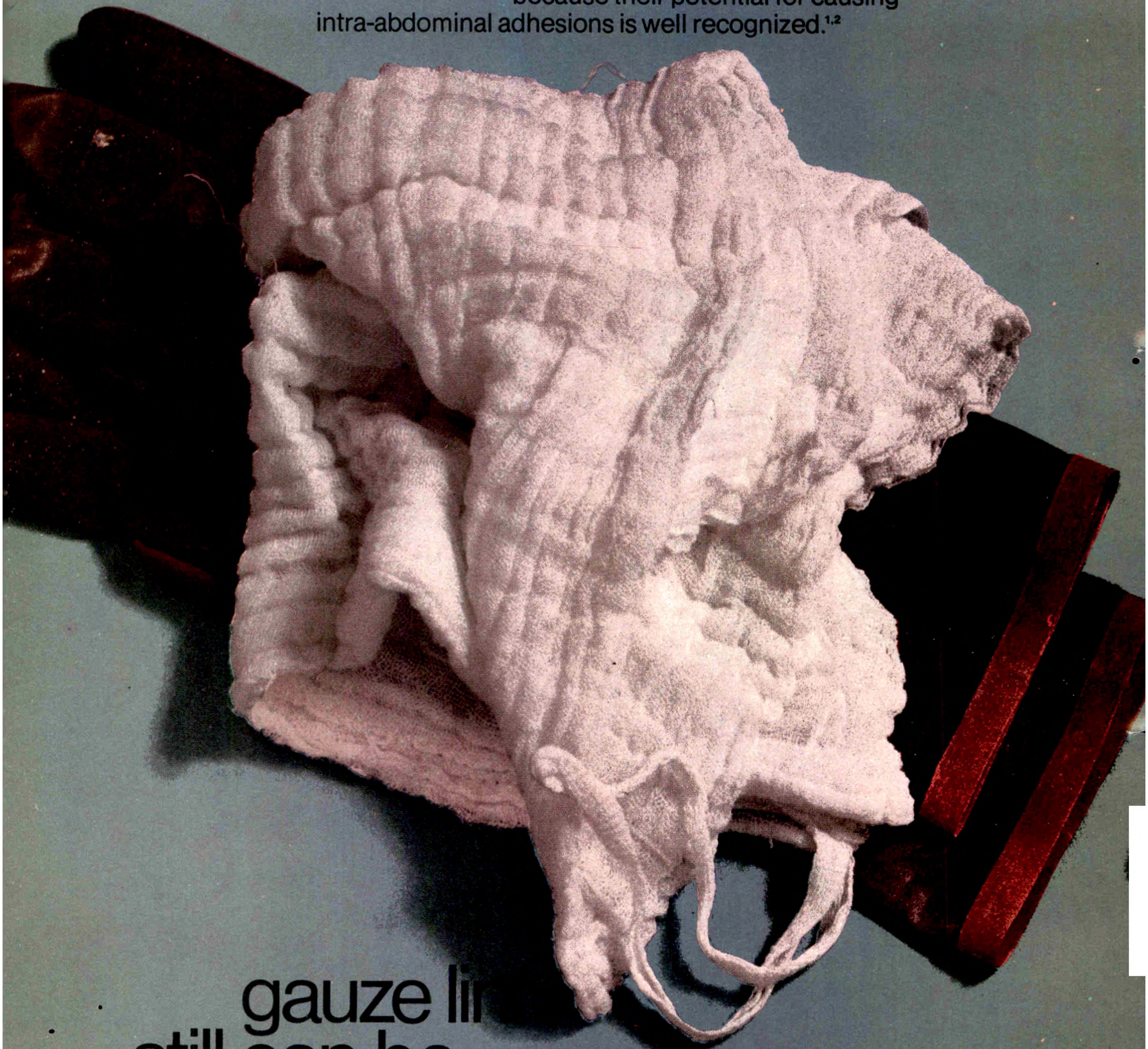

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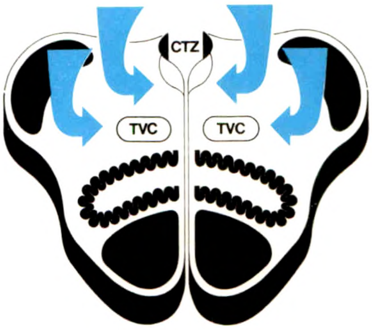

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Bendush, C.L., and Weber, R.: Clinical Results with Tobramycin Sulfate: A Summary of Worldwide Experience, J. Infect. Dis. (Supplement) (in press).

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BUN	21	43
Creatinine clearance	10	28
Casts	6	13
Blood urea	12	14
Albuminuria	1	4
Uric acid	1	0
WBC	1	5
RBC	0	5
	88 (in 53 patients)*	141 (in 105 patients)*

*Two patients are included in both categories; therefore, a total of 156 had 229 abnormal (related plus doubtful) adverse effects.

Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, have been reported with Nebcin, especially in patients on high dosage and/or prolonged therapy and particularly in those with known or suspected renal impairment. The accompanying table summarizes the renal effects found in the study group of 3,506 patients.

Nervous system: incidence of adverse effects

Adverse Reactions in the Nervous System

Condition	Number of Effects as Classified by Investigator	
	Related	Doubtful
Vestibular		
Dizziness	9	9
Vestibular disturbances	5	1
Nystagmus	2	0
Vertigo	2	0
Auditory		
Hearing decrease	5	1
Tinnitus	4	2
Temporary hearing loss	4	0
Headache	1	5
Taste	0	2
Apnea	0	1
Asthenia	0	1
Neuropathy (not specified)	0	1
	32 (in 23 patients)	23 (in 21 patients)

Adverse effects on both the vestibular and auditory branches of the eighth nerve can occur. Impairment of eighth-nerve function is most likely in patients with renal damage, especially in those on high dosage and/or prolonged therapy. Effects on vestibular and/or auditory function in the group of 3,506 patients are shown in the accompanying table.

In patients with normal renal function who do not receive Nebcin in higher doses or for longer periods of time than those recommended, the risk of toxic reactions is low. However, patients treated with Nebcin should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.

To maximize efficacy and minimize risk

1. Follow recommended dosage schedules for all patients; adjust dosage and/or dosage intervals in patients with impaired renal function.
2. Monitor patients whose renal function is initially normal but in whom oliguria or evidence of nitrogen retention (increasing serum creatinine, BUN, or NPN) develops during therapy.
3. Examine urine for an increase in protein, cells, and casts.
4. Monitor renal function in all high-risk patients—the elderly, debilitated, and those with impaired renal function caused by trauma, surgery, infection, or chemotherapy.
5. Monitor serum concentrations when feasible, and avoid prolonged levels above 12 mcg./ml. Determine serum concentrations if the dosage is increased above those usually recommended.
6. Assess auditory and vestibular function during prolonged treatment in patients with known or suspected renal impairment and in those with initially normal renal function who develop signs of renal dysfunction during therapy.
7. Avoid the concomitant or sequential use of drugs that are potentially ototoxic or nephrotoxic.

for serious gram-negative infections select Nebcin® ♦ I.M./I.V.

tobramycin sulfate

NEBCIN PEDIATRIC TOBRAMYCIN SULFATE INJECTION
20
NEBCIN® TOBRAMYCIN SULFATE INJECTION
80 mg. per 2 ml.
NEBCIN®
60 mg. per 1.5 ml.
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Lilly

Please see following page for summary of prescribing information.

Nebcin® ◆ I.M./I.V.
tobramycin sulfate

Summary of Prescribing Information

WARNINGS

Patients treated with Nebcin should be under close clinical observation, because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing ototoxicity and nephrotoxicity.

Both vestibular and auditory ototoxicity can occur. Eighth-nerve impairment may develop if patients have preexisting renal damage and if Nebcin is administered for longer periods or in higher doses than those recommended.

Tobramycin is potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by cylindruria, oliguria, proteinuria, or evidence of nitrogen retention (increasing BUN, NPN, or creatinine). Evidence of impairment in renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.

Nebcin should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.

In the case of overdosage or toxic reactions, peritoneal dialysis or hemodialysis will help remove tobramycin from the blood.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 12 mcg./ml. should be avoided. Urine should be examined for increased excretion of protein, cells, and casts.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, and vancomycin, should be avoided.

Nebcin should not be given concurrently with potent diuretics. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Description: Tobramycin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from the actinomycete *Streptomyces tenebrarius*. Nebcin Injection is a clear and colorless sterile aqueous solution for parenteral administration. It is stable and requires no refrigeration.

Indications and Usage: Nebcin is indicated for the treatment of serious infections caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa, Escherichia coli, Proteus* sp. (indole-positive and indole-negative), *Providencia, Klebsiella-Enterobacter-Serratia* group, *Citrobacter* sp., and staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).

Nebcin is indicated in the treatment of septicemia; central-nervous-system infections, including meningitis; neonatal sepsis; serious lower respiratory infections; gastrointestinal infections, including peritonitis; and serious skin, bone, and soft-tissue infections, including burns, caused by the susceptible organisms listed above. Clinical studies have shown Nebcin also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including Nebcin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity. Nebcin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Bacterial cultures should be obtained prior to and during treatment to isolate and identify etiologic organisms and to test their susceptibility to tobramycin. If susceptibility tests show that the causative organisms are resistant to tobramycin, other appropriate therapy should be instituted. In patients in whom gram-negative septicemia, neonatal sepsis, or meningitis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with Nebcin may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with Nebcin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the WARNINGS box above.

Contraindication: A history of hypersensitivity to tobramycin is a contraindication to its use.

Warnings: See WARNINGS box above.

Precautions: Specimens should be collected during therapy for examination, as recommended in the WARNINGS box.

Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of tobramycin (40 mg./Kg.). The possibility that prolonged or secondary apnea may occur should be considered if tobramycin is administered to anesthetized patients who are also receiving neuromuscular blocking agents, such as succinylcholine or tubocurarine.

Cross-allergenicity among aminoglycosides has bee

If overgrowth of nonsusceptible organisms occurs, a
be initiated.

Adverse Reactions: *Nephrotoxicity*—Renal function ch
BUN, NPN, and serum creatinine and by oliguria, cylin
proteinuria, have been reported, especially in patients
impairment who are treated for longer periods or with
recommended.

Neurotoxicity—Adverse effects on both the vestibula
of the eighth nerve have been noted, especially in patie
prolonged therapy. Symptoms include dizziness, vertig
ears, and hearing loss.

NOTE: The risk of toxic reactions is low in patients w
who do not receive Nebcin in higher doses or for longer
those recommended.

Other reported adverse reactions possibly related to
serum transaminase (SGOT, SGPT) and increased seru
granulocytopenia, and thrombocytopenia; and fever, r
nausea, vomiting, headache, and lethargy.

Suggested Dosage Guides—I.M./I.V.:

Usual dosage for adults, children, and older infants (no
3 mg./Kg./day administered in three equal doses ev
threatening situations, the dosage may be increased
administered in three or four equal doses. This dosa
3 mg./Kg./day as soon as clinically indicated. (Refer
dosage schedule.)

Dosage for neonates up to one week of age (normal ren
Up to 4 mg./Kg./day may be given in two equal dose
The usual duration of treatment is seven to ten days.

Dosage guidelines for adult or pediatric patients with re
After a loading dose of 1 mg./Kg., subsequent dosag
with reduced doses at eight-hour intervals or with no
intervals. To determine the reduced dose at eight-hou
ient nomogram in the package literature.* To calcula
prolonged intervals (if the creatinine clearance rate i
patient's condition is stable), the following formula m
1 mg./Kg. q. (6 × serum creatin
Neither regimen should be used when dialysis is bein

I.V. Administration—The usual volume of diluent for a
children, the volume of diluent should be proportionate
The diluted solution usually should be infused over a pe
minutes.

---

*An alternate rough guide for determining reduced dosage at eigh
whose steady-state serum creatinine values are known) is to divid
dose by the patient's serum creatinine.

Table 1. Dosage Schedule Guide for Adults with No
(Dosage at Eight-Hour Intervals

For Patient Weighing Kg.	Lb.	Usual Dose for Serious Infections 1 mg./Kg. q. 8 h. (Total, 3 mg./Kg./day) **mg./dose q. 8 h.**	**ml./dose**†	Ma Th **(Redu** 1 (To **mg.**
120	264	120 mg.	3 ml.	20
115	253	115 mg.	2.9 ml.	19
110	242	110 mg.	2.75 ml.	18
105	231	105 mg.	2.6 ml.	17
100	220	100 mg.	2.5 ml.	16
95	209	95 mg.	2.4 ml.	15
90	198	90 mg.	2.25 ml.	15
85	187	85 mg.	2.1 ml.	14
80	176	80 mg.	2 ml.	13
75	165	75 mg.	1.9 ml.	12
70	154	70 mg.	1.75 ml.	11
65	143	65 mg.	1.6 ml.	10
60	132	60 mg.	1.5 ml.	10
55	121	55 mg.	1.4 ml.	9
50	110	50 mg.	1.25 ml.	8
45	99	45 mg.	1.1 ml.	7
40	88	40 mg.	1 ml.	6

†Applicable to all product forms except Nebcin, Pediatric, Injectio

How Supplied: Ampoules Nebcin® (tobramycin sulfate,
(equivalent to tobramycin) per 2 ml., 2 ml., rubber-stopp

Ampoules Nebcin, Pediatric, Injection, 20 mg. (equiva
ml., 2 ml., rubber-stoppered.

Hyporets® (disposable syringes, Lilly) Nebcin Injectio
tobramycin) per 1.5 ml., 1.5 ml., and 80 mg. (equivalent
ml., 2 ml., in packages of 24.

Each ml. also contains 5 mg. phenol as a preservative,
fite, 0.1 mg. disodium edetate, and water for injection, q
sodium hydroxide may have been added to adjust the pH

Lilly

Additional information available
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The Kantrex®
(kanamycin sulfate)
record:

Percent in vitro susceptible to kanamycin*

	1970	1971	1972	1973	1974
E. coli	90.8	90.5	89.9	90.0	92.0
proteus sp.	89.5	89.5	88.4	90.0	91.0
klebsiella sp.	86.9	86.6	87.9	90.0	93.0
enterobacter sp.	90.5	90.1	90.2	91.4	92.0
serratia sp.	39.2	60.1	72.3	75.6	80.0
herellea sp.	83.2	86.8	87.0	88.4	91.0
mima sp.	78.1	73.9	76.5	74.4	78.0

*Susceptibility data from records based on over 250,000 isolates annually from 180 different hospitals. No in vivo correlation is claimed from the in vitro data.

In a world of changing bacterial challenges... a continuing record of bacterial susceptibility.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Combined Kantrex Injection and Pediatric Injection
(kanamycin sulfate injection)

For complete information, consult Official Package Circular.
(11) 6/18/74

Warning: Irreversible deafness can occur. Tinnitus or vertigo may also occur and indicate vestibular damage and impending deafness. The risk is sharply increased with renal dysfunction. In such cases, decrease size and frequency of doses. Discontinue kanamycin and check hearing if azotemia increases. Watch carefully for ototoxicity in older patients and patients receiving more than 15 Gm. of kanamycin. To avoid neuromuscular paralysis with respiratory depression, postpone intraperitoneal instillation in post-operative patients until recovery from anesthesia and muscle relaxants is complete. Although there have been isolated reports of respiratory depression following intraperitoneal instillation of kanamycin, there is no conclusive proof that this side effect can be produced with recommended doses of the drug. Avoid concurrent use of other ototoxic drugs including ethacrynic acid. Safety in pregnancy is not established.

Indications: Serious infections due to susceptible strains of E. coli, Proteus sp., E. aerogenes, K. pneumoniae, Serratia marcescens and Mima-Herellea. Culture and sensitivity studies should be performed.

Contraindications: A history of hypersensitivity to the drug. Prior auditory damage by kanamycin or other agents may be a contraindication if effective, alternative therapy is available.

Precautions: Obtain audiograms before and during therapy in patients with renal dysfunction when treatment lasts more than 5 days. Stop Kantrex if tinnitus or hearing loss occurs. Hydrate patients to prevent chemical irritation of the renal tubules. Assess renal function periodically, both before and during therapy. If signs of renal irritation occur (casts, cells, proteinuria), increase hydration and reduce the dosage or the frequency of dosage if necessary. In azotemic patients, the frequency (in hours) of doses may be obtained by multiplying the serum creatinine by 9. If azotemia or oliguria occur, discontinue therapy. Mycotic or bacterial superinfection may occur.

Adverse Reactions: Nephrotoxicity—albuminuria, presence of white and red cells, granular casts, azotemia and oliguria have been reported.

Ototoxicity—See Box Warning.

Irritation or pain at the injection site, skin rash, drug fever, headache and paresthesias.

Dosage and Administration: The usual dose is 7.5 mg./Kg./12 hours I.M. or I.V. The average adult dose is 1 Gm. daily. The maximum adult totai daily dose should not exceed 1.5 Gm. by all routes of administration and the total amount administered should not exceed 15 Gms.

The intravenous route is used only if intramuscular administration is not feasible. The 0.5 Gm. dose is added to 200 ml. of sterile diluent and administered 60-80 drips/minute.

When used as intraperitoneal instillation, the above dose is diluted in 20 ml. of sterile diluent. If possible, instillation should be postponed until after patient is fully recovered from effects of anesthesia and muscle-relaxing drugs.

As aerosol treatment, 250 mg. of Kantrex is diluted with 3 ml. of physiological saline and nebulize.

Kantrex Injection in concentrations of 0.25 percent (2.5 mg./ml.) has been used satisfactorily as an irrigating solution in abscess cavities, pleural spaces, peritoneal and ventricular cavities.

Supplied: Rubber capped vials as a ready-to-use sterile aqueous solution in two concentrations: 0.5 Gm. in 2 ml., 1.0 Gm. in 3 ml.

Pediatric Injection 75 mg. in 2 ml.

BRISTOL

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The open chest.

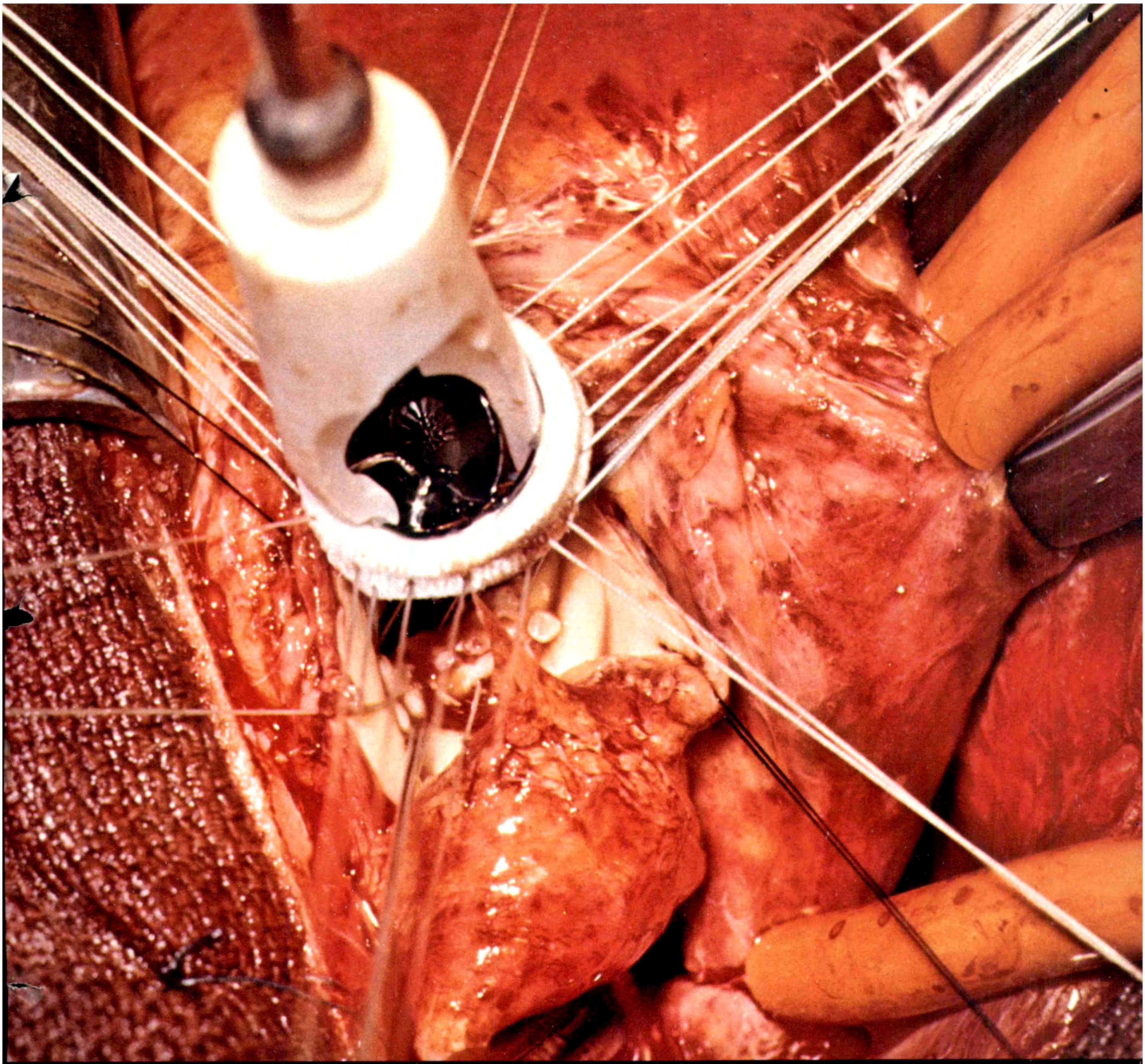
Another opening for staph*?

Postoperative surgical infections
Valve replacement: a procedure that can at once sustain life *and* predispose to infection. Although identification of the infectious organism may be difficult, a delay in treatment could result in invasion of the endocardium. The implicated organism may be a penicillinase-producing staph. Progression can be swift and devastating.

nitial antistaph therapy: injection
t's vitally important that effective treatment of bacterial invasion begin as soon as possible. f you suspect the presence of staph and must begin therapy before definitive culture results are known, Injection Unipen® (nafcillin sodium)† is a particularly suitable agent.

Appropriate specimens for bacteriologic studies to determine the causative organisms and their susceptibility to nafcillin should be taken prior to the first dose of antibiotic.† And, if those studies subsequently implicate organisms other than penicillinase-producing staphylococci sensitive to nafcillin, discontinue it and administer the appropriate antibiotic.

Rapid penetration
Unipen appears rapidly in plasma following intramuscular administration. Penetrates body tissues in high concentrations and diffuses well into pleural, pericardial and synovial fluids.



"On call" capability
Reconstitutes in less than 60 seconds. Remains stable for 24 hours.[‡]

Follow-up therapy: oral
Unipen (nafcillin sodium) is available in tablets, capsules, and oral solution as well as the parenteral form. The injectable form should be used initially in severe infections. And as soon as the clinical condition warrants, oral forms of Unipen allow you to continue antistaph therapy with the same antibiotic in a form more convenient to patients.

INJECTION AND ORAL
UNIPEN®
(nafcillin sodium)
as the monohydrate, buffered, Wyeth
Wyeth Laboratories
Philadelphia, Pa. 19101

See important information on next page. ▶

[*] Nafcillin-susceptible penicillinase-producing staphylococci.
[†] See Important Note on next page.
See important information under Parenteral Administration on next page.

Unipen®
(nafcillin sodium)

AS THE MONOHYDRATE, BUFFERED, WYETH

Disc Susceptibility Tests: Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure* has been recommended for use with discs for testing susceptibility to penicillinase-resistant penicillin-class antibiotics. Interpretations correlate diameters on the disc test with MIC values for penicillinase-resistant penicillins. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used, or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

*Bauer, A.W., Kirby, W.M.M., Sherris, J.C., and Turck, M.: Antibiotic Testing by a Standardized Single-Discs Method, Am. J. Clin. Pathol., 45:493, 1966; Standardized Disc Susceptibility Test, FEDERAL REGISTER 37:20527-29, 1972.

Indications: Although the principal indication for nafcillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to nafcillin sodium should be performed.

In serious, life-threatening infections, oral preparations of the penicillinase-resistant penicillins should not be relied on for initial therapy.

Important Note: When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of nafcillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to nafcillin sodium, the physician is advised to continue therapy with a drug other than nafcillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Methicillin is a compound that acts through a mechanism similar to that of nafcillin sodium against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in **in vitro** sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

Contraindications: A history of allergic reaction to any of the penicillins is a contraindication.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, appropriate therapy should be instituted, and discontinuation of nafcillin therapy considered. The usual agents (antihistamines, pressor amines, corticosteroids) should be readily available.

Precautions: As with any potent drug, periodic assessment of organ system function, including renal, hepatic and hematopoietic, should be made during prolonged therapy.

The possibility of bacterial and fungal overgrowth should be kept in mind during long-term therapy. If overgrowth of resistant organisms occurs, appropriate measures should be taken.

The oral route of administration should not be relied upon in patients with severe illness, or with nausea, vomiting, gastric dilatation, cardiospasm or intestinal hypermotility.

Safety for use in pregnancy has not been established.

Particular care should be taken with intravenous administration because of the possibility of thrombophlebitis.

Adverse Reactions: Reactions to nafcillin sodium have been infrequent and mild in nature. As with other penicillins, the possibility of an anaphylactic reaction or serum sickness-like reactions should be considered. A careful history should be taken. Patients with histories of hay fever, asthma, urticaria, or previous sensitivity to penicillin are more likely to react adversely.

The few reactions associated with the intramuscular use of nafcillin sodium have been skin rash, pruritus, and possible drug fever. As with other penicillins, reactions from oral use of the drug have included nausea, vomiting, diarrhea, urticaria, and pruritus.

Parenteral Administration: It is recommended that parenteral therapy be used initially in severe infections. The patient should be placed on oral therapy with this product as soon as the clinical condition warrants. Very severe infections may require very high doses.

Intravenous Route: The required amount of drug should be diluted in 15 to 30 ml. of Sterile Water for Injection, U.S.P., or Sodium Chloride Injection, U.S.P., and injected over a 5- to 10-minute period. This may be accomplished through the tubing of an intravenous infusion if desirable.

Stability studies on nafcillin sodium at concentrations of 2 mg/ml and 30 mg/ml in the following intravenous solutions indicate the drug will lose less than 10% activity at room temperature (70° F.) during the time period stipulated:

Isotonic sodium chloride	24 hours
5% dextrose in water	24 hours
5% dextrose in 0.4% sodium chloride solution	24 hours
Ringer's solution	24 hours
M/6 sodium lactate solution (conc. of 30 mg/ml)	24 hours

Discard any unused portions of intravenous solutions after 24 hours.

Only those solutions listed above should be used for the intravenous infusion of Unipen® (nafcillin sodium). The concentration of the antibiotic should fall within the range of 2 to 30 mg/ml. The drug concentrate and the rate and volume of the infusion should be adjusted so that the total dose of nafcillin is administered before the drug loses its stability in the solution in use.

There is no clinical experience available on the use of this agent in neonates or infants for this route of administration.

This route of administration should be used for relatively short-term therapy (24-48 hours) because of the occasional occurrence of thrombophlebitis, particularly in elderly patients.

Intramuscular Route: The clear solution should be administered by deep intragluteal injection immediately after reconstitution. After reconstitution, keep refrigerated (2°-8° C.) and use within 7 days or keep at room temperature (25° C.) and use within 3 days.

Oral Administration: Beta-hemolytic streptococcal infections should be treated for at least 10 days to prevent development of acute rheumatic fever or glomerulonephritis.

If oral therapy is inadequate, resort to parenteral nafcillin sodium.

After mixing, the oral solution must be stored in a refrigerator. Discard any unused portion after one week.

Supplied: INJECTION (VIALS)—Supplied in vial sizes of 500 mg., 1 gram, and 2 gram nafcillin sodium as the monohydrate, buffered. When reconstituted as recommended, the contents of each vial provides, respectively, 2-, 4- or 8-ml. of nafcillin sodium solution equivalent *per ml.* to 250 mg. nafcillin buffered with 10 mg. sodium citrate. Film-coated TABLETS—containing nafcillin sodium as the monohydrate, equivalent to 500 mg. nafcillin buffered with calcium carbonate. CAPSULES—containing nafcillin sodium, as the monohydrate, equivalent to 250 mg. nafcillin buffered with calcium carbonate. FOR ORAL SOLUTION—Combination pkg. of vial of dry nafcillin sodium as monohydrate and bottle of diluent—provides 80 ml. of solution containing equivalent of 250 mg. nafcillin per 5 ml. Alcohol 2%.

WYETH LABORATORIES PHILADELPHIA, PA.

Fundoplication for Reflux Esophagitis:

Misadventures with the Operation of Choice

HIRAM C. POLK, JR., M.D.

Fundoplication, whether performed by thoracic or abdominal approach, is a sound method for control of reflux esophagitis. A series of 312 operations have been reviewed to assess the frequency of complications and the methods by which these can be prevented or treated effectively. Each source of an untoward outcome is examined in detail, and suggestions as to prevention or recognition are advanced. The current low death and complication rates have been lowered even more by a conscious effort to refine the procedure further; such efforts have been associated with a failure rate of less than 5% in a mean followup of 4 years.

From the Department of Surgery and the Price Institute of Surgical Research, the University of Louisville School of Medicine, Health Sciences Center, Louisville, Kentucky 40201

THE OPERATIVE APPROACH to hiatal hernia and reflux esophagitis has evolved significantly both in concept and precept, particularly over the last decade. Indeed, the early operations oriented toward anatomic reconstruction of a hernial defect have been subjugated to the physiologic correction of the associated symptomatic abnormality, i.e., reflux esophagitis secondary to reflux of gastric acid. Although working independently, Nissen and Belsey and their respective colleagues[8,11] simultaneously turned to valvuloplasty operations to control the debilitating reflux of gastric acid into the lower esophagus. Anatomic hernia repair remained a secondary component of their procedures. Although this concept is more than a score of years old, only within the last decade has widespread acceptance been achieved. The clinical results associated with these operations include very reasonable morbidity and mortality and a substantial increase in efficacy and alleviation of symptoms, especially when compared to what had been achieved by anatomic reconstruction. Whereas a failure rate of 25% or more was common with operations devoted to restoring normal anatomy, failure rates of well under 10% are associated with the valvuloplasty procedures.

Impressive pre- and postoperative physiologic observations in man by DeMeester and associates[2] point to the significant beneficial effects of the fundoplication procedure (Nissen) with respect to the two other popular valvuloplasty operations. DeMeester's data derived from esophageal pH monitoring[1] clearly indicate the superiority of the fundoplication procedure as studied in his patients regarding acid reflux, minimal esophageal pH < 4, number of reflux episodes, esophageal motility, and distal esophageal sphincter pressure and length.

Our attention now turns to considering the adverse results of what is the operation of choice for a relatively prevalent disease. The purpose of this report is to describe a substantial personal experience with the operative procedure and to emphasize the adverse results so that those with less experience or those undertaking the procedure initially may eliminate these particularly painful, and perhaps now unnecessary, hazards.

Description of Over-All Experience

In prior studies reported by Zeppa and Polk,[9] only 90 fundoplication operations for reflux esophagitis were performed even though some 7,000 patients with hiatal hernia were diagnosed radiographically within their

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Presented at the Annual Meeting of the Southern Surgical Association, December 8–10, 1975, The Homestead, Hot Springs, Virginia.

TABLE 1. *Indications for Fundoplication for Reflux Esophagitis*

Intractable Esophagitis	92%
Dysphagia	3%
Co-existent Illness	2%
Acute Incarceration	1%
Pulmonary Aspiration	1%
Angina Syndrome	1%

medical center. During this experience at the University of Miami, very few procedures for this particular illness were performed by other surgeons. Whether this is a valid proportion of patients with hiatal hernia who warrant operation or not is a subject addressed previously.[9] The purpose here is only to qualify the experience from which this particular report is derived. The author's personal experience now numbers 312 operations performed for reflux esophagitis in which the principal component of repair was fundoplication. The prime indication for operation has been reflux esophagitis unresponsive to nonoperative management. Table 1 lists the specific indications for operation; there were 220 transabdominal operations and 92 performed by transthoracic incision. It is better to adapt the particular operative approach to the circumstances characterizing the patient in question, than for approach to be dictated by the surgeon's preference or limitations in technique.

Morbidity attending this operation is in part a function of the frequency of associated operations, categorized by transthoracic or transabdominal approaches (Table 2). The over-all morbidity is 14%. Three of the 312 patients died during hospitalization and are discussed in depth.

Operating time for fundoplication averaged just under two hours when performed by the transthoracic route and just under one hour when performed by the transabdominal route as an isolated procedure. Postoperative hospitalization averaged 8.2 days.

The ultimate measure of success is the consistent amelioration of symptoms. The initial 100 patients were studied in detail, with emphasis on repeated endoscopic studies (carried out frequently in the early postoperative period and less frequently thereafter) of the patients to confirm the continuing absence of esophagitis.[9] The failure rate with a mean followup of 3.8 years on the patients reported herein is 4.1%. Approximately half the failures related to primary anatomic recurrence of hernia, usually associated with gastroesophageal competence. However, the other half (2%) are more or less anatomically satisfactory but represent recurrence of reflux esophagitis. This early failure rate is highlighted by Nissen's earlier observation that most of his failures became apparent within three years of operation.[8] The failure rate in our first group of patients has not increased between the fourth and seventh postoperative years.

Adverse Results

Minor Problems

Among the less catastrophic misadventures which have generally not influenced either the long-term health of the patient or detracted from the over-all benefits of the operation is the vexing problem of incidental splenectomy. Indeed, when one must mobilize—occasionally in the face of prior operation—distal esophagus and proximal stomach, injury to the spleen occurs: 1) directly by the surgeon's instruments; 2) indirectly by retractors; 3) more commonly by traction medially and downward on the esophagogastric junction, producing capsular splenic tears. Seven per cent of patients have required treatment for unintentional injury to the spleen, partially justified by the wide exposure essential for fundoplication. Our initial response was that operatively injured spleens required excision. In recent years, following the lead of Hardy and Yelverton,[3] we have on four occasions found patients with limited and readily controlled capsular tears which could be treated by nonexcisional methods after release of the traction and careful attention to hemostasis in the splenic capsule. The late adverse effect of splenectomy in an often middle-aged to elderly adult population is not serious. However, the ultimately nonfatal complication of hiatal hernia repair in our experience has been subphrenic abscess. This has never occurred in the absence of splenectomy, although only two abscesses have followed the 20 splenectomies.

Operative wound infection has been an irregular product of this particular procedure, occurring more frequently in patients undergoing abdominal operations (Table 3). If data are adjusted for frequency of operations devoted only to the treatment of reflux esophagitis and hiatal hernia and excluding adjunctive procedures

TABLE 2. *Complications of Fundoplication*

Transabdominal Operations	220
Isolated for Esophagitis*	116
Systemic (4)	
Infection	
Wound (4)	
Deep (2)	
Includes Concomitant Procedures	104
Systemic (11)	
Infection	
Wound (7)	
Deep (2)	
Obstruction (1)	
Transthoracic Operations†	92
Systemic (7)	
Infection	
Wound (2)	
Atelectasis/Pneumonia (2)	
Local, Other (1)	

* Includes unintentional splenectomy.

† Includes both isolated and concomitant procedures.

for other illnesses, the percentage of operative wound infection becomes consistent with that in other clean operations. When an operative attack is aimed at reflux esophagitis alone, the operation is indeed a clean one, and none of the special measures known to control infection with potentially contaminated operations appears to be indicated.

A third nuisance has been dehiscence of the fundoplication, often discovered on some later radiographic studies. Hernial repair was maintained in 6 patients and gastroesophageal competence in 4 patients. In one patient, the fundoplication remained intact but slipped down around the midportion of the stomach, producing an hourglass gastric deformity unassociated with symptoms; it continues as such in that particular patient. At least two of the physiologic failures were associated with dehiscence of the fundoplication. Subsequently, we have replaced atraumatic gastrointestinal sutures of 3-0 silk used for the plication with 2-0 variety, eliminating dehiscence of the fundoplication. Whether this is a matter of suture bulk or improper placement is undetermined. We believe that we have consistently used deeply placed seromuscular sutures in the gastric fundus.

How does one insure that the fundoplication stays in place about the distal, intra-abdominal esophagus? If the fundoplication is of normal length and the left gastric artery does not have to be transected to provide exposure, the plication simply rests upon the insertion of the left gastric artery on the lesser curvature of the stomach. In some circumstances when that insertion is particularly low or when it has been necessary to transect this insertion, the fundoplication should be anchored at the lower portion of the now intra-abdominal esophagus. The most secure suture for this purpose should be placed at the *lower* border of the fundoplication where with the lowest plicating suture the stomach can be included very near the esophagogastric junction along the lesser curvature. Never have we secured the fundoplication to the diaphragm itself because these two components of esophagogastric competency function better independently.

The most frequent nuisance complication of fundoplication is transient dysphagia, typically appearing on the tenth postoperative day and disappearing by the twentieth postoperative day. Presumably, this results from local edema and the usual progression from a liquid to a solid diet over this period. Each of the 58 patients who developed this problem responded immediately when a liquid diet was maintained for two weeks and there was no recurrence of the dysphagia. Associated studies of evidence of vagal function carried out in a few such patients have indicated that inadvertent vagal injury is not responsible.

TABLE 3. *Wound Infection After Abdominal Fundoplication for Reflux Esophagitis*

Isolated Operations for Esophagitis		
With Splenectomy	3/18*	16%
Without Splenectomy	1/98	1%
Total	4/116	3%
Concomitant Operations†		
For Ulcer Disease	3/21	
For Biliary Tract Disease	1/28	
For Colonic Disease	1/5	
For Others	2/50	
Total	7/104	7%

* Two of the 20 splenectomies were associated with concomitant operations.

† Systemic antibiotics were frequently administered in the peri-operative period.

Judgmental errors also contribute significantly. Three patients who underwent laparotomy clearly would have had more adequate reconstruction and repair by the transthoracic approach; the reverse was recognized in one patient. On 6 occasions, ill-advised complementary procedures produced one early and 6 late complications. All procedures were vagotomy and drainage performed without clear-cut evidence of intractable duodenal ulcer disease. One of these patients represents the worst nonfatal complication in the series, his digestive disturbance leading to total disability after a variety of remedial operations. Failure to add myotomy in the presence of clear signs of disorders of esophageal motility mandated a secondary procedure in one patient.

Major Problems

Aside from those patients subjected to multiple, associated operations on a single occasion, major disasters accompanying fundoplication for hiatal hernia have only been associated with unintentional injury to the spleen, mobilization of an acutely inflamed esophagus, and other visceral injury.

A principal reason that a more conservative aproach to superficial splenic injuries has been taken in recent patients is that the only subphrenic abscesses in this series followed splenectomy for what seemed to be minor trauma. One patient had a very long course with the first manifestation of his undrained abscess being atrial fibrillation.[5] Indeed, the final component of this particular patient's abscess was drained through the left lower quadrant, necessitating a three-month hospitalization.

Since the two deaths associated with early operation for severe edematous, weeping esophagitis (vide infra), the three additional patients with this disease were treated by insertion of a small nasal tube and a continuous antacid drip to induce relative healing of the acutely inflamed organ. Resolution of the inflammatory process has alway been demonstrated on repeated study within a week when the antacid is given faithfully. Within another week, operation can be undertaken with sufficient resolution of the inflammatory process to make handling of the acutely inflamed organ surgically safe.

Another special problem concerns the management of the patient with Schatzki ring formation.[10] Such apparent ring formation in most patients is spastic, unassociated with an organic obstruction, and readily disappears following operative control of the reflux. However, in none of the four patients requiring excision of a fibrotic ring have we experienced particular difficulty approaching the excision of the fibrotic ring by high gastrotomy. Esophageal fistula relating to excision of a fibrotic Schatzki ring through an esophagotomy has occurred. The obvious lesson is that such lesions should be dealt with by transversely placed proximal gastrotomy just below the esophagogastric junction. The diaphragmatic narrowing can be prolapsed into the stomach, excised readily, and esophageal mucosal continuity restored if this is the preference; simple healing occurs regularly without mucosal suture, provided reflux is terminated.

Hospital Deaths

Of the three patients who died, the first was a 55-year-old man with disabling severe reflux esophagitis producing intractable pain. An acutely weeping esophagus was identified endoscopically, and barium study disclosed an active duodenal ulcer. This patient also had severe rheumatoid arthritis, treated with systemic corticosteroids. He underwent a transabdominal exploration which confirmed the presence of a duodenal ulcer. During excision of a segment of the posterior vagus, the acutely inflamed peri-esophageal tissue began to bleed, and an opening in the posterior aspect of the esophagus was made. The esophagus was then gently mobilized downward, but in doing so an additional rent was made in the esophagus. Bleeding from the left gastric artery was encountered and controlled. Fundoplication was completed and esophageal repair buttressed with the plication at the sites of injury. Pyloroplasty and gastrostomy were also added. The patient developed signs of bilateral bronchopneumonia in the presence of prior co-existing chronic obstructive emphysema. Although alimentary function was normal, he developed a fulminant gram negative pneumonitis. Present-day respiratory support was not available, and despite tracheostomy and repeated bronchoscopy the patient died of progressive pneumonitis. In retrospect, the duration of operation required because of injury to the acutely inflamed esophagus certainly prolonged anesthesia. At no time did the local problem associated with his severely inflamed esophagus appear to contribute to his death.

The second patient was a 62-year-old man with an 18-year history of esophageal reflux with severe esophagitis unresponsive to prior vagotomy and pyloroplasty. Preoperative evaluation showed an acutely weeping, inflamed esophagus with apparent shortening. Transthoracic operation disclosed the particularly tenuous nature of the esophagus. Although the esophagus was not injured, gentle handling did induce bleeding in the peri-esophageal tissues and a lengthy dissection up to the aorta to the left chest was undertaken to restore the esophagogastric junction to its subdiaphragmatic position. Fundoplication was otherwise completed normally. The patient did well for three days but then became profoundly ill. Chest films showed evidence of fluid and air in the left chest. A clinical diagnosis of esophageal disruption was made and immediate reoperation undertaken. Dissolution of about two-thirds of the circumference of the lower third of the esophagus was found. This distal esophagus at the level of the diaphragm was transected and a gastrostomy inserted. The remaining esophagus was excised, the residual stump drained, the chest closed and a cervical esophagostomy constructed. However, the patient died within 24 hours of operation from the effect of uncontrolled infection despite aggressive management with fluids, antibiotics, and a full range of supportive methods.

The third patient, known to have arteriosclerotic heart disease, sustained a fatal myocardial infarct on his eighth postoperative day.

Incomplete Relief of Symptoms

Among results which represent less than the maximal benefit expected from the operation, the most impressive is the patient who had the right operation for the wrong illness. Despite the stringent nature of our indications for operation, we are convinced in retrospect that operations on at least two occasions were performed for individuals with diseases other than reflux esophagitis. A classic example was a businessman who had presented with angina-like syndromes and had had three normal coronary arteriograms. Clinical signs of reflux became more noticeable with the classic increase in discomfort associated with reclining, leaning over, or increasing intra-abdominal pressure. Subsequent studies indicated that acid perfusion of the distal esophagus did produce the electrocardiographic abnormalities associated with his earlier signs of cardiac ischemia, a syndrome described by Morris and associates.[7] He underwent an uneventful operative repair and a benign postoperative course. An obstructive episode occurred on the eighteenth postoperative day, and although this episode resolved, the patient experienced continuing chest pain. He was readmitted to the hospital a year postoperatively with a documented myocardial infarct. He is also the only patient who continues to have late dysphagia. Radiographic studies show rotation of the plication, initial emptying of the esophagus into the plicated fundus and only subsequently, in ruminant fashion, into the rest of the stomach. Careful studies still have not explained this problem totally. However, this subsequent myocardial infarct, although well tolerated and associated with a return to work, makes the risk of revision measurable, all the more so because he has learned to tolerate the complication.

This individual represents an adverse outcome from the confusion of coronary artery disease with reflux esophagitis. There are four other individuals who were evaluated for reflux esophagitis following careful cardiologic evaluation and normal coronary arteriogram. All were documented to have reflux esophagitis and have subsequently been entirely relieved of their complaints following fundoplication.

Alleged Problems

Six per cent of our patients have complained of upper abdominal fullness and discomfort after eating in the early postoperative period, consistent with the "gas bloat" syndrome described by Woodward and colleagues.[13] In all of these patients but one, symptoms disappeared within 3 months. Most patients who are ill of reflux esophagitis learn to swallow repeatedly to facilitate the acid-clearing mechanism.[12] Incident to repeated swallowing, the patients became aerophagic. However, when it continues after gastroesophageal competence is restored, gaseous distention of the upper abdomen ensues. Among the 18 patients so afflicted, in only one did this problem persist more than 3 months, and he has had mild but continuing discomfort over a period of 5 years. The gas bloat syndrome has occurred much less frequently than described by Woodward and colleagues,[13] although we have been unable to define the reason. Perhaps it is not related to the size of the esophageal lumen but rather to the looseness and the freedom with which the fundoplicated segment lies about the restored intra-abdominal esophagus. In this series, at least two fingers, and in some cases the surgeon's entire hand, could be passed underneath the plication alongside the esophagus. This loosely applied fundic wrap probably allows most patients to belch after a short time postoperatively; more tightly constructed fundoplications may not.

Other Problems

Dealing with a stenotic esophagus secondary to reflux esophagitis continues to be a major challenge. Hollenbeck and Woodward[4] have found that fundoplication employed as an onlay graft to widen the narrowed esophagus is highly efficacious. However, as pointed out previously,[4] the so-called Nissen-Thal operation[8] has been a uniform disaster for us. A limited trial was undertaken because of greater risk reported for intestinal interposition, despite superb long-term physiologic results of this later procedure. However, we have now reverted to the management of the patient with fibrous stricture by jejunal interposition after the method of Merendino and Dillard[6] because of our inability to match Woodward's results in these difficult cases.

We continue to treat most soft or pliable strictures by dilatation and fundolication. Among 13 such patients, dilatation one to three times has always been sufficient if the reflux is controlled effectively by the plication.

Esophageal shortening that is so apparent in some patients with reflux esophagitis proves real in only a minority; in only 10 patients was the apparent shortening genuine. This represents a relative indication for the transthoracic approach allowing thorough mobilization of the esophagus. In the past, we have left the plication about the esophagus in the thorax and accepted evidence that it was not essential, although desirable, to restore the esophagogastric junction to the abdomen in every instance. We believed that plication was so efficacious in preventing reflux that restoration of abdominal esophageal length was unnecessary. Our attempts in four patients have been unsatisfactory. Accordingly, every effort is now made in these circumstances to restore the esophagogastric junction to an infradiaphragmatic position.

Discussion

This presentation describes both real and imagined difficulties with fundoplication, using a substantial experience to define ways to avoid or preclude the seeming misadventures. The technical maturity achieved with the operative procedure is such that relative risks of these procedures can be defined narrowly. Morbidity in the last 100 patients has declined from 14 to 5%, and no deaths have occurred among the last 158 patients undergoing such operations.

Whether the criteria for this operation have been too rigid and too narrow is a constant concern. As the operation has proved itself, perhaps it deserves wider applicability. Certainly a determinant of the relative indication for any operation is its risk-to-reward ratio. However, as long as dysphagia does not supervene, we believe that the patient with mild reflux esophagitis is best managed nonoperatively; only those patients who have persistent complaints unresponsive over long periods warrant operative intervention.

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DISCUSSION

DR. THOMAS BOMBECK (Chicago): In Dr. Polk's excellent presentation of a very large series of Nissen fundoplications, I must say that we could not agree more. We have been involved in studying this particular problem for the last eight years at the University of Illinois. We have essentially the same incidence of success with this procedure; that is, it always prevents reflux when it remains intact. We do have an incidence of gas bloat syndrome somewhat higher than he has reported, but lower than that reported by Dr. Woodward.

I wish to ask him if he would please describe for us the specific tricks that he uses in preventing gas bloat syndrome in these patients, enabling the patient to belch postoperatively.

DR. ROBERT ZEPPA (Miami, Florida): There are a number of points which I think deserve some amplification.

The first is: In terms of the splenectomy problem associated with this operation, we have found that in some patients who have particularly short, short gastrics, where the stomach is attached very, very tightly to the spleen, taking those down allows for freedom of the fundus, and allows you to do a very safe wrap without damage to the spleen.

Secondly, in terms of the stent in the esophagus—and we use this in particular as a teaching device for our residents. We pass a 46 Maloney dilator into the stomach, and then do the wrap around that, to ensure that they will not cinch up the lower esophageal segment, like Aunt Tillie's girdle, because that's not the purpose of the operation. The purpose of the operation is to obtain the rather salubrious contact between the lower esophageal segment and intragastric pressure.

This can be accomplished with a very loose wrap around the lower esophageal segment. In fact, we have been able, with the help of our colleague, Dr. Arvey Rogers in the Department of Medicine, to confirm Dr. DeMeester's elegant findings in terms of the changes in lower esophageal segment pressure in these patients after surgery.

Despite this, a number of our patients do complain of excessive gas over the period of three to four months, when they are becoming accustomed to a rather new gastrointestinal (gastroesophageal) anatomical relationship.

The other point I'd like to make is that, in the last several years, we have been placed in contact with patients who do not have esophagitis, by any stretch of the imagination; but these are patients with very, very highly uncontrolled reflux, and we have seen it primarily in women. Age ranges from the late 20's on up into the 60's. In the younger age group, these are women who, having toddlers, bending over to pick them up, will lose breakfast, lunch, or whatever the prior meal was at the time of picking up these youngsters.

This is an incapacitating problem, and in this athletic age, with some of these women playing tennis, even on forehand shots they'll lose gastric content. The Nissen fundoplication is a superb procedure for this control, and we have used that, I think, with a greater degree of efficacy than in any other cohort of patients on whom we have applied this procedure.

One more point: We are a bit slower than Dr. Polk to operate, I would guess, since he has accumulated now somewhat over 300 patients, and when he left Miami we were at the figure that he had given you. We're still operating on about one out of every hundred patients who has demonstrated reflux in our institution. Perhaps it's because we deal with a very large cohort in our community of well-intentioned and talented gastroenterologists, who control these patients very effectively; so that when we see the patients, we have two problems: Uncontrolled reflux, or esophagitis.

DR. DONALD L. PAULSON (Dallas): I rise to talk about another operation of choice for gastroesophageal reflux; namely, the combined Belsey and Collis gastroplasty procedures. We have no quarrel with the Nissen fundoplastic procedure, and do congratulate Dr. Polk on the excellence of his results.

(Slide) We reviewed our experience from 1963 to 1970, in 1971, with 760 cases of a type of fundoplication modified on the Belsey principle. As you see, we had clinical relief of symptoms in about 95% of the patients. As the end of three months, by cinefluorography of the esophagus and the water siphon test, we had a 5% incidence of persisting gastroesophageal reflux, and at a year an additional 4% so-called recurrent reflux. These are all failures, so at a year we might say that we had 90% good results.

In following these cases for a period up to seven years, there is a 2% increment of recurrence of gastroesophageal reflux per year.

On the basis of these failures, and appreciating the fact that with gastroesophageal reflux there is esophagitis in a high percentage of these patients, with consequent varying degrees of esophageal shortening, and following the lead of Mr. J. Leigh Collis in Birmingham, England, and Pearson in Toronto, we began to use this combined procedure.

(Slide) As you see, the procedure is simply a lengthening of the esophagus by the Collis gastroplasty, using the Maloney bougies, size 50 to 54, in the esophagus, through the esophagogastric junction, and making a gastric columnar lined tube of the lesser curvature of the magenstrasse of the stomach. This is carefully constructed to make a tube of the desired diameter, with not too patulous an opening.

This division can extend for a distance of 6 cm or more, depending upon the length of tube desired for lengthening of the esophagus.

(Slide) It results in a connecting tube between the esophagus and the new esophagogastric junction. Both sides of the gastroplasty are sutured, or the stapler can be used.

(Slide) A modified fundoplication is then done approximating the fundus of the stomach, or the cardia, to the anterior lateral surface of the tube, through at least two thirds to three fourths of its circumference, with the Maloney bougie in place to avoid compromise of the lumen.

(Slide) This illustrates a case with a stricture at this point (indicating) esophageal shortening, an incarcerated pouch of the hernia above the diaphragm.

(Slide) This is a better film showing the stricture. 23% of our 163 cases done by this technique had definite esophageal strictures, with shortening.

(Slide) This is the postoperative result, with the esophagus actually extending to this point, (indicating) this being the Collis tube below the hiatus.

There is very definite evidence that shortening of the esophagus is a key factor in the failure to correct gastroesophageal reflux, and that the success of these operations, as we have done them, depends upon obtaining a sufficient length in the subdiaphragmatic position.

At present, our indication is to perform this combined procedure for any degree of shortening secondary to esophagitis, particularly with strictures, and for all second operations for gastroesophageal reflux, recurrences in our own cases or cases performed by others.

In addition, because of the high incidence of pulmonary complications in these cases, we have performed it for all of these cases with pure respiratory symptoms. There has been no increased morbidity or mortality and correction of reflux in 95% of the cases in a followup period of one to five years.

Dr. Edward R. Woodward (Gainesville, Florida): We also have had problems with infection, and have had two deaths directly related to this complication. In one patient, a small capsular tear of the spleen caused us to do a splenectomy followed by subphrenic abscess. Although this was promptly drained, the patient had delayed blowout of the ligated splenic artery, and met a rather rapid and bloody demise. The second fatal case was a mediastinal abscess that we were very slow to recognize, not expecting it after a transabdominal procedure; and even though drained, the patient continued to have a septic course and expired.

I think the answer is that the fundus is so thin that our sutures in the fundoplication routinely go into the lumen. Many of these patients are hypochlorhydric, and have pathogenic organisms which are transmitted via the suture from the gastric lumen to the peritoneal cavity; and I think it is not as sterile a procedure as we would like to think.

I agree that we are probably unnecessarily removing some of these minor injuries to the spleen, and that a Gelfoam patch on a small capsular tear is probably adequate.

We would have a minor disagreement, I think, over the use of the transthoracic approach. We use it very freely, as he does, for essentially the same indications. However, particularly when there has been acquired shortening, we routinely leave the repair above the diaphragm. We reduce it to a comfortable length, and then carefully suture the diaphragm to the endothoracic fundus. We have clinical information, supported very solidly by manometric and cineradiographic studies, showing that the valvuloplastic effect of the fundoplication is just as good as if the repair were reduced below the diaphragm. I think it is far better to leave it without tension above the diaphragm. Without careful repair, however, parahiatal hernia can occur, and we have seen five such complications.

The gas bloat syndrome—everybody seems to think that we must cinch our repairs awfully tight, or that we don't know how to pass bougies. I assure you that we make ours as loose as anybody else's. We don't see it as often now. The main reason is that in the primary case, with moderate, uncomplicated esophagitis, we prefer the Hill repair. May I remind you that the present Hill repair includes a valvuloplastic element, a semi-Belsey maneuver, and in our hands this restores lower esophageal competence almost but not quite as thoroughly as the Nissen fundoplication. The side effects are literally negligible after this operation, and we personally feel that this is the primary operation of choice for gastroesophageal reflux.

We continue to disagree rather thoroughly over transmural strictures, and we now have used the Thal-Nissen method in over sixty cases without a mortality and with 85% good results. We feel that the resective approach should be reserved for the Thal-Nissen failures.

We also have seen Nissen wraps come completely undone and have no good explanation. It is, fortunately, quite rare. We have also seen the repair slip down onto the body of the stomach, causing an hourglass constriction; the repair should definitely be fixed to the esophageal wall.

We concur that the Nissen principle is clearly the most certain to correct gastroesophageal reflux.

Dr. Richard R. Crutcher (Lexington, Kentucky): I rise to enthusiastically endorse the Nissen fundoplication that Dr. Polk has reported on. In 80 cases, I did a similar procedure in the first half of the cases, but without fundoplication. The recurrence rate was 10% and gastroesophageal reflux was 40% as demonstrated by x-ray examination. In the last half of the cases, nothing was added to the technique except fundoplication by the Nissen method. In this group, with a followup x-ray one year or more postoperative, there has been no recurrence of hernia, and only one patient was found to have gastroesophageal reflux by x-ray. I might add that the patients have no symptoms of gastroesophageal reflux.

A few points of technique that I think are important: I prefer the abdominal approach. Using the automatic intern that Dr. Woodward mentioned this morning—we call it "the upper hand"—the anterior wall of the chest can be retracted upward, so an excellent exposure of this area can be obtained. As for injury to the spleen, if no sharp retractors are used in the peritoneal cavity, I don't think you'll have many ruptures of the spleen. I use nothing except a sponge holder with sponge to retract the spleen out of the way.

The fundoplication must be loose, and if you have it loose enough so you can put a finger alongside the esophagus, then you are not apt to have constriction.

There are two other important points in technique: One is to anchor the esophagus to the rim of the diaphragmatic hiatus. The second is to suture the wrapped-around fundus of the stomach to the esophagus. These two steps will prevent telescoping of the wrapped-around stomach downward as the esophagus tries to retract upward into the chest cavity. I believe this probably accounts for a good bit of the postoperative bloat syndrome and dysphagia. This has certainly not been a problem in my patients.

I'd like to ask Dr. Polk whether he has had this experience: A significant number of patients that I see are sent to me for cholecystectomy. On careful questioning, I find that many really have more symptoms referable to their hiatal hernia and reflux than they do to the gallbaldder, even though they have stones in the gallbladder. Therefore, I think it's most important to repair the hernia at the time the cholescystectomy is done.

Dr. John L. Sawyers (Nashville): I certainly agree with Dr. Polk that operation for hiatal hernia is indicated only in patients with moderate to severe reflux esophagitis, and also agree that the best operative procedure is valvuloplasty, to correct reflux of gastric juice into the esophagus. In our experience, the Nissen fundoplication has given the best results of the commonly used operative procedures for correction of esophageal reflux.

I commend Dr. Polk for presenting to us this careful analysis of his large personal experience with fundoplication, and his courage in bringing to our attention the misadventures that are associated with the operation. However, I think that his results are really very good, and certainly the low complication rates in his last 158 patients are to be envied.

Our most frequent complication following the Nissen fundoplication has been temporary dysphagia, but we have encountered this rarely in recent years, since we routinely insert a No. 44 French Maloney esophageal dilator. In addition to doing the fundoplication around the esophagus with this large dilator in place, we make the plication loose enough to insert a finger between the fundus and the esophagus.

It is important to test the effect of the valvuloplasty at the operating table. We have done this by a simple test that has been described by others. After temporarily occluding the pylorus, 250 cc of saline is injected into the stomach through a nasogastric tube. The tube is pulled back up into the esophagus, and the stomach is squeezed like a bagpipe to see if saline refluxes out through the nasogastric tube. If no saline comes out of the tube, we can consider the valvuloplasty to be effective. If saline does come through the tube, additional sutures are taken.

DR. HIRAM C. POLK, JR. (Closing discussion): Dr. Bombeck asked: What do you do specifically to avoid the gas-bloat syndrome? I think a little of this, actually, is discussing it with the patient, and letting him realize, both preoperatively and in the early postoperative days, that aerophagia is a common phenomenon, that it must be combatted, and when they have the tendency or the impulse to swallow, they ought to try to control this.

I agree with Dr. Zeppa in the sense that we have tried to provide a loose wraparound, as has been stated here repeatedly. I'm not sure that's the entire answer, but the gas-bloat syndrome certainly has been an uncommon phenomenon in our experience.

Dr. Zeppa asked about the problem of taking down the short gastrics. We have had to do this in something just under 5% of the cases we've treated. It's fairly uncommon, because usually, once you mobilize the posterior wall of the stomach, there is enough room to do this nicely. Indeed, we make that wraparound so very loose that more often than not one can pass the four fingers or his hand underneath that plication alongside the esophagus, maintaining a very loose function and effective valve.

Dr. Paulson reported to me that they have, with the Collis-Pearson procedure, actually had no deaths, no complications, and no splenectomies. So I suppose that is a real advantage. I would worry about those suture lines, and think, in my hands, they'd probably leak, one way or another.

Clearly, this practice would have avoided one of our three deaths: the patient who had dissolution of the esophagus after a lengthy esophageal mobilization to get it under the diaphragm.

The problem that Dr. Woodward discussed, of leaving the stomach in the thorax, has been a concern for us. Dr. Leslie Pearlstein, one of our senior residents, reviewed our experience with this. I assure you, as noted in the discussion of Dr. Woodward's paper at the American Surgical, we had more complications in four patients in whom we tried to leave the fundus in the chest than Dr. Woodward was able to achieve in sixty patients.

So it's just the particular circumstance that we don't do that operation very well, and I'm sure that we have something to learn from Gainesville. There is still the problem of the gas-bloat syndrome. It can be eliminated in Miami and Louisville, but not midway in between.

The real point, objectively, is to look to Dr. DeMeester's data. I recommend it to you, because it's a very objective, physiologic study of the relative merits of the fundoplasty operations and how they are achieved.

Someone asked: How do you control the dehiscence of the fundoplication? We have changed progressively from 4-0 to 3-0 to 2-0 silk for the plicating sutures themselves, because, when we reoperated on one of these patients, the sutures had simply broken. They were not pulled out of the tissue; they had broken. I suppose those seromuscular sutures ought to be of 2-0 silk.

Dr. John Sawyer's smooth Tennessee approach to patient rapport is very impressive, in which he implies that splenectomy may indeed be part of the operation. That may well be the legal approach. I think an even better point that he made, particularly for those of you who start to do this operation, will be to test the efficacy of the valvuloplasty. We have not done that routinely, but, of course, we have long since developed a feel for what works and what doesn't work. His concept about putting in fluid and seeing if you can produce reflux is a particularly good one, and would be even better if you monitored esophageal reflux intraoperatively.

Dr. Crutcher asked: How do you deal with the patient who has cholelithiasis and a hiatal hernia? We go back to our basic indication, and that's of course esophagoscopy. If esophagitis is present, we will repair the hiatal hernia and excise the gallbladder. If it's absent, as we have described in a prior paper, we would be quite willing to watch the hiatal hernia and excise only the gallbladder.

A Current Appraisal of Problems with Gangrenous Bowel

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Gangrenous bowel most often results from hernia, adhesions and mesenteric insufficiency. The overall mortality rate for 151 cases was 37%. This figure was 20% for hernia, 23% for adhesions and 74% for mesenteric insufficiency. In the latter category where bowel resection was feasable the mortality rate was 40%. Other causes of bowel gangrene had a mortality rate of 28%. In many instances the pathophysiologic processes were of such a nature that current medical expertise has not reached a level of development to effectively cope with the situation. There were, however, a significant number of cases where survival may have been achieved had it not been for deficiences on the part of the patient, the primary health care personnel or those in attendence at the referral center. The basic keystone for a successful outcome in the management of patients with the gangrenous bowel problem is early surgical intervention. All will be lost if patient exposure to this source of lethal toxins is allowed to proceed to an irreversible stage. Liberal antibiotic administration probably postpones the arrival of intractable hypotension. Other factors which can be expected to improve the survival rate include minimization of technical errors, repair of incidental hernias, elemination of dependence upon nasogastric tubes for the definitive management of patients with complete bowel obstruction (with one or two exceptions), and a firm commitment to the diligent pursuit and early definitive management of postoperative complications.

SINCE THE TURN of the century, there has been a sustained decline in mortality rate among patients suffering from bowel obstruction. Most of this improvement has been observed in the area of simple obstruction, where circulatory compromise was not a factor. Unfortunately, an equivalent degree of improvement has not been obtained where gangrenous bowel complicated the problem (Table 1). The purpose of this study was to critically examine the records of 151 patients with bowel gangrene who were treated in our hospital over the past 20 years. Cases included in this series were limited to those where gangrenous bowel was resected at operation or demonstrated at postmortem examination. The overall mortality for the entire group was 37%. Twenty-one of these cases resulted from a variety of miscellaneous conditions including intussusception, carcinomatosis, annular pancreas, diverticulitis, congenital reduplication, pancreatitis and volvulus. The mortality rate among this group was 28%. The remaining 130 cases (86%) had gangrenous bowel as a result of hernia (45 cases), adhesions (43 cases) or mesenteric insufficiency (42 cases) (Table 2). Because of the variety of clinical and pathophysiologic characteristics among these three categories, it was elected to examine them under separate headings.

Hernia

The forty-five cases in this group were almost evenly divided between males (24 cases) and female (21 cases). The mortality rate among those 20 cases under 50 years of age was 5% in contrast to the remainder where this figure was 23% (Table 3).

The most common hernia responsible for bowel gangrene was the inguinal variety (Table 4). The mortality among these 22 patients was 14%. The incisional and umbilical category was productive of a considerably higher mortality rate of 21%. Perhaps this is related to the type of patient who usually harbors such a hernia. They are often obese and diabetes is present with a relatively high frequency. Femoral hernia was responsible for bowel gangrene in only three incidences, but the dangerous potential for these lesions is exemplified by a mortality rate of 66%. One would suspect that early surgical

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TABLE 1. *Results Achieved in Managment of Gangrenous Bowel Problems*

Date	Author	Category	No. Cases	Mortality
1950	Becker[6]	Strangulation	176	24%
1952	Nemir[9]	Adhesions	11	27%
		Hernia	10	50%
1962	Silen[11]	Adhesions	56	23%
1965	Leffall[8]	Adhesions	29	17%
		Hernia	16	37%
1975	Barnett	Adhesions	43	23%
		Hernia	45	20%
1967	Ottinger[10]	Mesenteric Insufficiency	136	92%
1974	Skinner[12]	Mesenteric Insufficiency	33	85%
1975	Barnett	Mesenteric Insufficiency	42	74%

TABLE 2. *Distribution Among the More Frequent Etiologic Conditions of Bowel Gangrene*

Etiology	No. Cases	% of Total Cases	
Hernia	45	30	86%
Adhesions	43	28	
Mesenteric Insufficiency	42	28	
Other Causes	21	14	
Total	151		

intervention for those cases with gangrenous bowel resulting from hernia would be productive of the better survival rate. This position was supported by the fact that 21 cases were operated upon within 36 hours or less and the mortality rate was 5%. The 16 cases operated upon after a longer preoperative time interval, experienced a mortality rate of 25% (Table 5). It was difficult to correlate the length of resected bowel with survival rate. Of interest was the fact that none of the patients who lost bowel segments longer that 100 cm failed to survive (Table 7). The usually severe clinical symptoms resulting from such a lesion may precipitate earlier surgical intervention. The overall mortality for the 45 cases experiencing bowel gangrene from hernia was 20%. Among the 30 cases which were managed before 1965, the mortality rate was 23% while this figure dropped to 13% for the 15 cases treated after this date. The records of the 9 fatalities were examined carefully to determine the circumstances which prevailed. There were three cases where better care in our hospital may have resulted in survival. One patient developed a perforated duodenal ulcer in the postoperative period. This was not expeditiously diagnosed and the patient expired. The second patient was admitted with a large scrotal hernia. He was operated upon for another condition and during the postoperative period the hernia became strangulated with resultant gangrene and death. The third case was a very obese patient who presented with clinical and x-ray evidence of intestinal obstruction along with a past history of peritonitis from a ruptured appendix. A strangulated, gangrenous femoral hernia was discovered 30 hours later. Had these patients been correctly diagnosed and treated, the mortality rate for the entire series may have been 13%. Additionally, two of the remaining fatalities were possibly salvagable, but their management was not under our control. One was observed for an irreducible hernia for four days in a local hospital before being transferred. He died within 30 minutes after arrival in our emergency room. The other case was a similar situation, treated for 5 days before being transferred for definitive treatment. It was not beyond the realm of possibility, then, to have obtained a mortality rate of 9% in this group of patients. Additional lowering of the mortality rate was probably not possible (Table 7). The remaining 4 patients died as a result of extensive congenital anomalies (1 case), progressive, extensive mesenteric venous thromboses (2 cases) and heart failure (1 case).

Adhesion

There were 24 females and 19 males among these patients. The mortality rate was 15% for the 19 patients who were less than 50 years of age and 29% for those above 50 years (Table 3). There were 28 cases managed before 1965 with a mortality of 21%. Those seen after this date numbered 15 and resulted in a mortality of 26%.

TABLE 3. *Age Distribution Related to Mortality*

	Hernia			Adhesions			Mesenteric Insufficiency		
	No. Cases	%	Mortality	No. Cases	%	Mortality	No. Cases	%	Mortality
50 years of age or less	20	45	5%	19	44	15%	9	20	66%
Over 50 years of age	25	55	23%	24	56	29%	33	80	76%

TABLE 4. *Hernias Responsible for Bowel Gangrene*

Hernia	No. Cases	Mortality
Inguinal	22	14%
Incisional and Umbilical	14	21%
Internal	5	0%
Femoral	3	66%
Spigelian	1	0%
Total	45	20%

The mortality rate achieved among 13 patients who were operated upon within 36 hours from the onset of symptoms was 8%. Where operation was instituted with a greater than 36 hour delay, 24% failed to survive (Table 5). When 100 cm of bowel or less was resected (20 cases) the mortality rate was 25%. Resection of longer segments of bowel (20 cases) revealed a mortality rate of 10% (Table 6). The overall mortality rate for the 43 cases was 23%. There were four possibly preventable deaths which were under our control (Table 7). Two of these cases were managed with long nasogastric tube suction for extended periods of time allowing the development of bowel gangrene with irreversible shock. One patient died from leakage at the site of closure of an inadvertent enterostomy. The remaining patient died from postoperative hemorrhage as evidenced by an abdominal cavity filled with blood at postmortem examination. It would have been possible to achieve a mortality rate of 13% had the above mentioned complications been avoided. Among the fatalities, there were 4 cases of complete bowel obstruction which were treated nonoperatively at home or in other hospitals for 3 to 5 days. They had all reached an irreversable stage from bowel gangrene by the time they arrived in our emergency room. Nevertheless, those were probably preventable deaths or must be considered so until proven otherwise. There were two patients suffering from bowel gangrene which we considered to be nonsalvagable. One had extensive abdominal carcinomatosis and the other died of emphysema and diabetic complications two weeks after surgery. We conclude that a mortality rate of 4% may have been possible among these 43 patients with gangrenous bowel resulting from adhesions.

Mesenteric Insufficiency

There were 42 cases in which bowel gangrene resulted from some form of mesenteric circulatory insufficiency. These included arterial embolism, arterial thrombosis, venous thrombosis or low blood flow to the bowel in the absence of vessel occlusion. The diagnosis was made at postmortem examination in 8 cases while 34 received surgical exploration. Among the latter group, 8 cases were closed without additional surgical effort. The remaining 26 cases underwent bowel resection with or without operative maneuvers directed toward restoration of blood flow. There were 28 males and 14 females in this group. Thirty-three (80%) of the cases were past 50 years of age (Table 3). Among those patients (8 cases) where surgical intervention was employed within 35 hours, the mortality rate was 37%. When a longer time interval elapsed (25 cases) the mortality rate was 76% (Table V). Among the 27 cases where bowel was resected, 7 cases received removal of a segment of 125 cm or less with a mortality rate of 43%. When the resected segment exceeded this length (20 cases) the mortality rate was 65% (Table 6). The overall mortality for the 42 cases was 74% (Table 7). Three cases could have been managed more expeditiously with possible lowering of the mortality rate to 67%. One patient was observed for more than 36 hours with a mistaken diagnosis of pancreatitis. A second patient also sustained inordinate delay before receiving surgery. The third patient died because of complications from an abdominal vascular procedure carried out the day before. The entire small bowel was found to be gangrenous at postmortem examination. The remaining 28 patients were considered to be unsalvagable in view of current medical expertise. Nineteen patients exhibited gangrene from the duodenum to the rectum. Six patients died of severe cardiac problems. One patient each was lost because of extensive abdominal tumors, hepatic coma and pulmonary embolism combined with extensive gangrene. Among the 27 cases where bowel resection was carried out, the mortality rate was 40%.

Discussion

Over the years we have developed a position of firm advocacy in favor of the use of antibiotics in patients

TABLE 5. *Mortality Rate Related to Time From Onset of Symptoms to Operation*

	Hernia			Adhesions			Mesenteric Insufficiency		
	No. Cases	Deaths	Mortality Rate	No. Cases	Deaths	Mortality Rate	No. Cases	Deaths	Mortality Rate
36 Hours or less	21	1	5%	13	1	8%	8	3	37%
More than 36 hours	16	4	25%	25	6	24%	25	19	76%
Total Cases	37			38			33		

TABLE 6. *Mortality Rate Related to the Length of Bowel Resected*

Length of Bowel Resected (cm)	Hernia			Adhesions		
	No. Cases	Deaths	Mortality Rate	No. Cases	Deaths	Mortality Rate
0–100	32	6	18%	20	5	25%
More than 100	6	0	0%	20	2	10%

with intestinal obstruction.[1] Being persuaded that bacterial organisms play a major role in the development of progressive and irreversible hypotension during exposure to gangrenous bowel, we think that antibiotics may significantly postpone the arrival of the irreversible stage. They provide considerable protection against emerging bacteremia and may extend the life of bowel where there is borderline circulation.[2] Among the antibiotics with which we have had experience, cephalothin and kanamycin have been satisfactory.[3]

The relative frequency of external hernia versus adhesions as a cause of bowel obstruction has evidenced a progressive reversal: formerly the external hernia was the most common etiologic agent, now adhesions have taken over the lead, especially in the western world. One would think that external hernia would provide a very favorable circumstance for early surgical intervention and effective management of the bowel gangrenous problem. Such has not been effectively realized. Some of the deaths resulted from inordinate delay between the time of onset of symptoms and presentation of the patient for definitive surgical management. Responsibility appears to be divided between patient and primary health care personnel. The entire responsibility does not rest here, though, because external hernias have remained undiscovered for extended periods after arrival at referral centers. The femoral hernia especially may pose a challenge in this respect since large, obvious masses are not characteristic of the condition. The danger is further compounded in the obese patient with generous skin folds and thick layers of adipose tissue. Another variety, the Richter's hernia, may provide an even more subtile lesion culminating in gangrene with all the lethal potential characteristics of this condition. Perhaps these factors may be related to our especially high mortality rate with femoral hernias. Of the patients who were operated upon within 36 hours, 5% died. Past this period, the corresponding figure was 25%. Incisional and umbilical hernias yielded a mortality rate of 21%. There was a high incidence of obesity and diabetes among this group of patients. The infirmities related to these problems possibly contribute to an explanation of the lower survival rate. Another complication observed after bowel resection consisted of progressive venous thrombosis after bowel resection. It would seem that blood clotting is initiated at the peripheral site of division of the veins and then propagates centrally until those vessels draining the normal bowel are obstructed with progressive infarction of the remaining intestine. The prospect of routine heparinization of all those patients as a prophylactic measure is somehow not overwhelmingly attractive. Our findings suggest that the longer the segment of circulatory embarrassed bowel involved in the hernias, the better the chances for survival. When the amount was less than 100 cm the mortality rate was 18%. Resection of segments longer than this resulted in no mortality. Perhaps the severe, hemodynamic changes, which occur from the extensive lesions, prompts earlier surgical intervention and the shock of oliguric origin can be effectively treated with volume restoration. Another factor of considerable significance in influencing survival is the age of the patient. Our patients under 50 years of age experienced a mortality rate of 5% while 23% of those who were beyond this age group failed to survive.

TABLE 7. *Results Among 130 Cases of Bowel Gangrene*

Etiology	No. Cases	Mortality		
		Actual	Possible for Us to Achieve	Possible
Adhesions	43	23%	13%	4%
Hernia	45	20%	13%	9%
Total	88	21.5%	13%	6.5%
Mesenteric Insufficiency	42	74%	67%	67%

Gangrenous bowel resulting from adhesions provides an even more dangerous set of circumstances than the conditions which attend strangulated hernia with gangrene. The neck of the hernia sac, which is tight enough to occlude the mesenteric blood supply, will usually disallow the passage of toxic materials into the general peritoneal cavity. In most circumstances of bowel gangrene resulting from adhesions, the entire visceral and parietal peritoneal surfaces are exposed to highly lethal material, heavily laden with bacteria and toxins which they generate. Experimental studies have shown that any of the various intra-abdominal surfaces, including the omentum, is capable of absorbing a lethal dose of this material.[7] The principle of early operative intervention with removal of devitalized bowel, as with external hernia, must be the fundamental keystone around which any successful surgical therapeutic program is constructed. Episodes of hypotension must be astutely avoided as there is ample evidence that this problem increases susceptibly to the toxins emanating from gangrenous bowel.[4] Among our patients, those who were operated upon within 36 hours of the onset of symptoms experienced a mortality rate of 8%. Where the period of delay was longer than this interval the fatality rate was 24%. Why has the successful clinical application of this principle been so difficult to achieve? It is true that certain findings may favor the diagnosis of bowel gangrene. These include severe, unrelenting abdominal pain, tachycardia, fever, abdominal tenderness, abdominal rigidity, leukocytosis, localized abdominal distention, and a palpable mass. Wangensteen's admonition, "There are no absolute criteria by which simple and gangrenous bowel obstruction can be differentiated with finality, short of operation" is true today and must be honored if maximal survival rates are to be achieved. Becker[5] conclusively and finally laid to rest the notion that the two conditions could be distinguished regularly by employing the clinical criteria available during the preoperative period. The patient harboring gangrenous bowel may present with gut obstruction and evident peritonitis. These individuals will have positive x-ray signs of obstruction and this along with the characteristic findings of peritonitis will usually motivate the physician to proceed with surgical intervention. All cases do not present these findings. Some may appear with signs of peritonitis, but in the absence of x-ray findings of obstruction. The practice of treating peritonitis of uncertain etiology nonoperatively might afford the opportunity for irreversible exposure to bacteria and their products because of delay. Then, the possibility also exists that the presenting findings may suggest only intestinal obstruction without evidence of peritoneal irritation. These circumstances may prevail, because of the involvement of a relatively short segment of bowel which might be well protected by surrounding loops of small bowel, and not allow sufficient exposure to precipitate clinical signs. For these reasons we are persuaded that a commitment to the operative management of all cases of complete mechanical bowel obstruction, with one or two exceptions, should be made as soon as the diagnosis is apparent. Judicious decisions must be made between earlier surgical management to terminate exposure to gangrenous bowel toxins versus the utilization of adequate preoperative preperation in order to afford maximum fluid and electrolyte repair to improve the patient as a surgical risk. Appropriate antibiotic administration can play a useful role in gaining more time during the preoperative period, but this approach must not be abused. We no longer employ nasogastric suction tubes, long or short, as the definitive management of complete non-inflammatory, mechanical bowel obstruction. These modalities are of value in the management of partial bowel obstruction, postoperative inflammatory obstruction, paralytic ileus and as an adjunct to surgery in the management of complete bowel obstruction. As with hernia, several of our cases arrived at our hospital after too long a delay as a result of procrastination on the part of the patient or primary health care personnel. Then there were some preventable complications, the responsibility for which must rest upon our shoulders.

Gangrenous bowel problems associated with mesenteric insufficiency are attended by the poorest survival rates of the more common etiologic categories. The majority of these patients are elderly and have other problems which complicate the issue. Advanced atherosclerosis, myocardial disease and diabetes are not uncommon. The diagnosis of threatened bowel viability is not easy to establish in the absence of lumen occlusion, and this is especially true early in the course of the illnesses. The patient who is threatened with this malady must receive intensive support from the beginning. Volume restoration must be kept at an optimal level.[4] Heparinization should be strongly considered. Antibiotics are best started early in the course of the illness.[3] An angiogram involving the superior mesenteric radicles should be obtained. If it shows an area of arterial occlusion, then operative intervention is in order. When the bowel is exposed at surgery, the frankly gangrenous segments should be immediately resected. Like hernias and adhesions, the earlier surgical resection is carried out, the better the chances for survival. In some instances, arterial embolectomy or bypass connections from the superior mesenteric artery to the aorta will reverse toward normal a segment of bowel that appeared to be marginal. Monitoring of the localization of radioactive material and temperature changes in the bowel wall have been alleged to be of value in establishing viability.[12] The second look operation 24 hours later has been helpful in some circumstances where bowel survival could not be predicted at the time of the initial procedure. In spite of these modalities, it is too often that irreversible gangrene is demonstrated from the duodenum to the rectum and a hopeless situation exists. Or a successful surgical procedure is followed by demise from cardiac or pulmonary lesions.

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DISCUSSION

DR. WATTS R. WEBB (Syracuse, New York): I'd like to share with you a recent series of ours which I think bears out very beautifully the lessons that Dr. Barnett has brought to our attention.

This was a series recently analyzed by Dr. Bruce Chamberlain and Dr. Shatilla, from the Community Hospital, in Syracuse. This is a private hospital, and so we were not dealing with the urban indigent, and there are very few of the stoic, reluctant rural patients that give you a completely different caliber to the patients that you are seeing.

These were 103 consecutive cases over the past eight years of mechanical small bowel obstruction. These did exclude those patients who had vascular obstruction, such as the mesenteric thrombosis.

It turned out, of this group, that 50 were strangulated, and 53 were simple obstructions. There were no deaths in the simple obstructions. There were two deaths in the strangulated group, both unrelated to toxic effects; one, an anesthetic problem, and the other, a late bronchopneumonia.

I think the important thing that came out of this was, again, to re-emphasize what Dr. Barnett said, and had been mentioned by Dr. Wangensteen before, that there are no differential characteristics or criteria by which one can separate simple from strangulated bowel early. Whether you look at the fever, the tachycardia, the enzymes, the physical examination for tenderness or rebound tenderness or rigidity, or whether you look at the bowel by x-ray, including barium studies, there was no way to make a differentiation early between simple and strangulated bowel. Late, obviously, you can make it from looking at patients from across the room; but early, there was no way.

Secondly, these patients came—and I think this is probably one of the most important things that was emphasized by Dr. Barnett—from an enlightened group of internists and family physicians, who got them to the surgeon very early in the course of their illness. Essentially all of them who were operated were operated in the first few hours; few as long as 24 hours after arriving in the hospital. There was a brief period of very rapid physiologic resuscitation, with fluids and whatever else was required, including massive antibiotic therapy for the enteric organisms, both aerobic and anaerobic, and then early operation.

There were very few resections. Very few of these patients had gangrenous bowel, because they did get to surgery early, and they were operated early. And this, I think, is the real key to reducing the mortality rate in the strangulated group down to 4%, as Dr. Barnett had predicted you should be able to do.

I think the only ones that we now believe should be handled definitively with a long tube would be, perhaps, those that have carcinomatosis, that have radiation fibrosis, or perhaps those that have already had multiple operations for recurrent obstruction from adhesions. The incidence of gangrene in this group is very, very low, and usually one has opportunity to resuscitate them, treat them with a long tube, and then watch them for other problems as they develop.

DR. JONATHAN E. RHOADS (Philadelphia): I think you will agree that Dr. Barnett and his coauthors have done a very thorough analysis of a large experience with this vexing problem. He did not tell us how many patients they had intercepted early enough so that they didn't require resection, and, no doubt, were saved. He began with those which had to be resected. So his figures are necessarily higher.

Now, I used the term "vexing" because the results with these conditions have failed to improve in the way one would expect them to have improved, with the many gains in supportive care now applied in clinical practice. Perhaps one must look for some countervailing trends. I will cite three which I suspect may play an adverse role.

The first is the increasing reluctance to use laparotomy as a diagnostic tool. Dr. Dever used to say: "We will now dispel mystery and reveal truth," and proceed to lay the abdomen open. We are so cowed by the possible charge of doing unnecessary operations that we will often wait substantial periods of time in the hope of establishing a secure diagnosis by other means in a patient who presents with a significant possibility of housing a catastrophe.

Second, we have been bombarded with propaganda about preoperative preparation of patients, making up blood volume deficits and correcting fluid and electrolyte deficits. These are important, but with a large bore needle, they can be well advanced in about the same hour or two that it usually takes to get the patient on an operating table. One needs a prompt 24-hour-a-day laboratory, and one needs the realization that total restoration is not a prerequisite to starting the operation. Fifty per cent restoration will usually do, and the second 50% perhaps can be completed more safely a little slowly.

Third, and more applicable to the patients with vascular disease, one needs to be very reluctant to conclude that the patient is hopeless. Some, of course, are hopeless, but with the application of intravenous hyperalimentation to patients with short bowel syndrome, it is surprising how little intestine will suffice for long-term survival.

If, during the first 60 days, nutrition is provided parenterally, the remaining bowel has time to adapt, and has the nutrients it needs for hypertrophy. Dudrick and his associates have had ten patients with 18 inches or less of small bowel whom they have treated successfully in this way.

DR. JUDSON G. RANDOLPH (Washington, D.C.): I would like to agree with Dr. Barnett fully on the premise that only with the immediate removal of gangrenous bowel, when it can be successfully done, are we going to beat this problem, when it involves reasonable lengths of bowel.

I'd like to remind all of you, however, that when most or all of the bowel is involved, some quite different advice might be offered.

I was fortunate, as a junior house officer to be present when Robb Rutledge, of this society, in 1957 did the first mesenteric embolectomy. When I saw him put all that green, black, blue, and purple bowel back into the abdomen, I thought my hero had taken leave of his senses. And yet it did prove that with a second-look approach to this kind of massive bowel insult, a lot of the bowel changed in 48 hours. We have had the experience now in 12 cases with children, entirely, that showed that surgeons who are loath to leave any discolored bowel in the abdomen may actually be taking out viable bowel. In the interest of occasionally preventing the short gut syndrome, I'd like to just show you an illustrative case.

(Slide) This is the appearance of the bowel of a 15-year-old boy who had had an ileal conduit. He already had very markedly reduced renal function, and as you can see, there is nothing wrong with his bowel.

When the bowel is blue or purple, or thick, edematous (slide)—such as in this slide—in a child 15 years old with severely damaged kidneys, so that we were sure that his biochemistry would not support the couple of loops of jejunum that he had that were of adequate color, this was all untwisted and returned to the abdominal cavity.

This shows that 48 hours later we took out the limp, flaccid black and green bowel, and left still an awful lot of terrible looking bowel which we thought had a chance to survive, and brought it out with stomas.

(Slide) This shows this bowel seven weeks later, when we were putting it back together; and this youngster is quite healthy now.

(Slide) This shows the kind of patient in whom we would do this now. This is a volvulus in a baby. We put all that bowel back, and expect, and hope, that much of it would regain function.

Several years ago, in discussing this at the University of Virginia, President Muller's institution, Dr. Ben Eiseman was there at the same time I was, as a visitor, and he said: But don't you have a horror of having feces in the abdominal cavity?

I said to him, as I think we should underscore with these remarks, that there is already diapedesis of organisms through the bowel, and, I think, in the interest of a chance of the bowel recovering in some of these massive insults, that we should do the second-look procedure in about 48 hours.

Dr. Arthur I. Chenoweth (Birmingham, Alabama): One of the points I was going to make was to make reference to the parenteral hyperalimentation, which is of such tremendous help to all patients who need to be operated on for intestinal obstruction.

The other two were to make a reference to the use of tubes. This subject has been generally touched upon, but to elaborate a bit on the use of the long tube, one of the well-known football coaches has often said that when you put the ball in the air for a pass, three things can happen, and two of them are bad. I think almost the same thing might be said for the use of the long tube in the preoperative phase, when considering the matter of small bowel obstruction.

In the first place, it's often not possible to get it inserted to its effective depth, and time is lost in this effort. Second, once it's down, the stricture can be masked, as has been mentioned before. On the other hand, there are certain indications for its use, and one of them is, after operation for adhesions has been carried out, a number of times one is faced with the necessity for lysing these adhesions again. One of our members, Dr. Raleigh White, in about 1955, suggested the use of a long tube already in place to serve as a stent for the loops of bowel in a benign position to prevent further recurrence.

I can't leave without making reference to Dr. Joel Baker's presentation at one of these meetings in about '62 or '3, when he presented the use of his long tube for decompression of the bowel, which is of inestimable value. The tube in question, as most of you know, is simply a long Foley catheter. And this is most effective in decompression, and can be left in place as a jejunostomy.

I think that the presence of this tube in everybody's operating room is almost a necessity, for it is needed occasionally.

Dr. William O. Barnett (Closing discussion): We would support Dr. Chenoweth's position related to the use of a long tube as a stent for recurrent bowel obstruction. We utilize the Baker tube in our practice.

I would like to thank Dr. Webb for his comments. He contibuted to the management of some of the cases included in our series.

Dr. Rhoads' remarks are always welcomed. The cases included in this paper had irreversible gangrene and those which were suspicious initially, but returned to normal after release of the obstructing mechanism, were not included. We would certainly agree with Dr. Randolph that the second-look procedure is of value in those cases where extensive ischemia or significant alteration of the bowel has occurred. Under these circumstances, removal of a portion of the altered bowel would not represent a logical approach. Continued support of the intestinal tract in situ might represent the only hope for survival, as slim as it might be. This position is not to be confused with the firm principle of always removing lesser segments of gangrenous or questionable bowel.

Timing of surgical intervention in a patient who harbors gangrenous bowel continues to represent a considerable challenge. The major problem relates to achieving early surgical intervention to decrease the exposure time to toxic materials versus taking sufficient preoperative time to avail the patient to the advantages of optimal, preoperative fluid and electrolyte restoration.

Finally, we continue to practice thorough irrigation of the peritoneal cavity where contamination has occurred. Also intraperitoneal and systemic antibiotics are utilized for we are persuaded that in some cases these agents may be decisive in favor of survival.

Use of Aminoglycosides in Surgical Infections

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Most infections on the surgical ward are due to one or more gram-negative rods, acting either as the sole pathogens or as principal components in a polymicrobial flora. To date, parenteral aminoglycosides have proven to be the most effective antibiotics for control or treatment of such sepsis. Unfortunately, however, serious complications as well as therapeutic failures do occur.

During a 40-month period, 405 surgical patients receiving aminoglycosides (Gentamicin, Tobramycin, Sisomicin, or Amikacin) were prospectively studied with respect to: indications for the antibiotic; patient population; serum concentrations of antibiotic according to route of administration, dose in mg/kg/day, and renal function; rapidity of antibiotic excretion in the urine; causative bacteria and their sensitivities to each aminoglycoside as determined by both disc and tube dilution methods; severity and frequency of drug complications; and clinical efficacy of each study antibiotic.

Results supported the contention of a superior effectiveness from aminoglycosides for established abdominal and unspecified surgical infections, more rapid development of therapeutic blood levels by intravenous administration, need to alter drug dose according to frequent serum creatinine determinations, increased drug toxicity in dehydrated and shocked patients, preventability of complicating Candida sepsis, and the importance of early as well as adequate surgical debridement and drainage.

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THE MAJORITY of infections on any surgical ward are usually due to one or more of the gram-negative bacilli.[7] Such pathogens either act singly, as is the case with most hospital acquired infections, or instead participate in the creation of a bacterial synergism by combining with various other aerobic species and, perhaps even more commonly, with a multitude of heretofore seldom recognized anaerobes.[6] Although surgical therapy in the form of abscess drainage, debridement of necrotic tissue, or other procedure is unquestionably important, antibiotics nevertheless play a significant role in the overall control of sepsis. Of the different groups of antimicrobials that have been used to treat these infections, aminoglycosides have proven to be the most reliably effective of all such agents.[7]

During the 40-month period ending 30 April 1975, 405 patients on the Trauma, Burn, and Pediatric Surgical Services at Grady Memorial Hospital received one or more courses of therapy with a parenteral aminoglycoside. During the first 4-month period, Tobramycin was the antibiotic almost routinely selected. Thereafter, in three equal 12-month intervals, the antibiotics administered were, respectively: a randomization (according to odd and even hospital numbers) between Tobramycin and Gentamicin; Sisomicin alone; and similar randomization between Amikacin and Gentamicin. Criteria demanded for case inclusion in the study were: 1) a presumed or already proven gram-negative infection which could at least potentially be cultured; and 2) a drug permission form signed by either the informed patient himself or an appropriate family member or guardian.

Procedures

The usual dose of Gentamicin, Sisomicin and Tobramycin was 1 mg per kilogram of body weight, administered intramuscularly or intravenously every 8 hours.[7] That for Amikacin, an antibiotic closely akin to Kanamycin, was 5 mg per kg of body weight, given similarly and according to the same time schedule. Any impairment in renal function dictated a longer interval between times of antibiotic administration, with the serum creatinine

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Supported by grants from Eli Lilly and Company, the Schering Corporation, and Bristol Laboratories.

TABLE 1. *Response of Infections to Aminoglycoside Therapy*

	Number of Patients	Apparent Cure	Controlled, Then Recurred	No Response	Candida Sepsis	Indeterminate Cases
Generalized peritonitis	201	185	9	6	1	—
Intra-abdominal abscess	96	84	5	3	4	—
Cholecystitis/cholangitis	17	14	—	2	—	1
Burn Wound Sepsis*	30	14	5	3	8	—
Other Wound Infections*	23	18	1	3	1	—
Pneumonia/empyema*	15	8	2	4	—	1
Miscellaneous	23	12	2	1	—	8
Totals	405	335	24	22	14	10

* Significantly poorer response to therapy than other categories (P = 0.05)

being used as the multiplying factor. For example, a serum creatinine of 3 mg% indicated that the aminoglycoside should be given only every 24 hours, that is, 8 hours multiplied by the serum creatinine of three.

Whenever possible, cultures of the foci responsible for sepsis were processed by anaerobic as well as aerobic techniques. Even though speciation was accomplished for both, antibiotic sensitivities generally were run only on the aerobic isolates. Both disc[1] and tube dilution[4] methods for antibiotic susceptibility were employed.

Patients were monitored for effectiveness of antibiotic in controlling or eliminating the infection, pharmacology of each drug with respect to blood levels and urinary excretion,[8] and potential for aminoglycoside toxicity:[2,3,7] The latter included routine blood counts, basic liver function tests, evaluation of renal function (urine analysis, blood urea nitrogen, serum creatinine, and clearances of both urea and creatinine), and tests for function of the eighth cranial nerve (audiograms and electronystagmograms).[2] An attempt was made to obtain such studies prior to, during, and after therapy in each case; yet this was not always possible. The clinical course of the patient and benefits of specific surgical procedures were also recorded.

After completion of therapy, analyses were made in order to determine antibiotic efficacy and safety. Other factors, such as ideal dosage of the several aminoglycosides, importance of host resistance, and proper role of surgery, were likewise considered.

Results

The average age for the 405 patients was 34 years, with a range of 10 months to 89 years. There were 309 Negroes, 95 Caucasians, and one American Indian. The sex ratio was 258 males to 147 females. No significant differences were noted between the individual antibiotic categories.

The majority of patients had peritoneal infections, with 201 cases of generalized peritonitis and 96 with intra-abdominal abscesses (Table 1). Sepsis arising from a burn or other wound accounted for an additional 53 patients. Infections of the biliary tract, lung, and various other areas made up the remaining 55 cases. The distribution of forms of sepsis among the several study antibiotics did not vary significantly, that is with the single exception that Amikacin was administered only half as frequently as were the other antimicrobials (Table 2).

Pharmacology

Antibiotic therapy was given for an average of 10 days, with a range varying from three to 29 days. In general, previously stated goals of antibiotic dosage and frequency of administration were routinely met.

Blood levels achieved with Gentamicin, Sisomicin, and Tobramycin were quite similar (Fig. 1). Following an intramuscular injection of 1 mg/kg of body weight, serum concentrations averaged 2.2 mcg/ml at 2 hours,

TABLE 2. *Response of Sepsis to Aminoglycoside Therapy*

	Number of Patients	Apparent Cure	Controlled, Then Recurred	No Response	Candida Sepsis	Indeterminate Cases
Tobramycin	129	103	8	6	8†	4
Gentamicin	107	91	6	5	3	2
Sisomicin	114	100	6	5	1	2
Amikacin	55	41	4	6*	2	2
Totals	405	335	24	22	14	10

* Significantly lower response rate with Amikacin (P = 0.05).
† Significantly greater incidence of complicating Candida sepsis (P = 0.05).

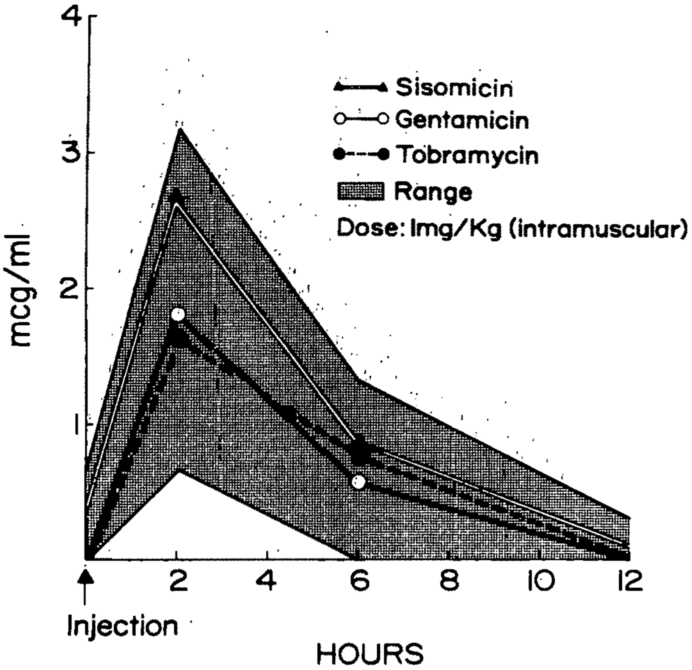

FIG. 1. Average serum concentrations of aminoglycoside following an intramuscular injection at a dose of 1mg/kg body weight.

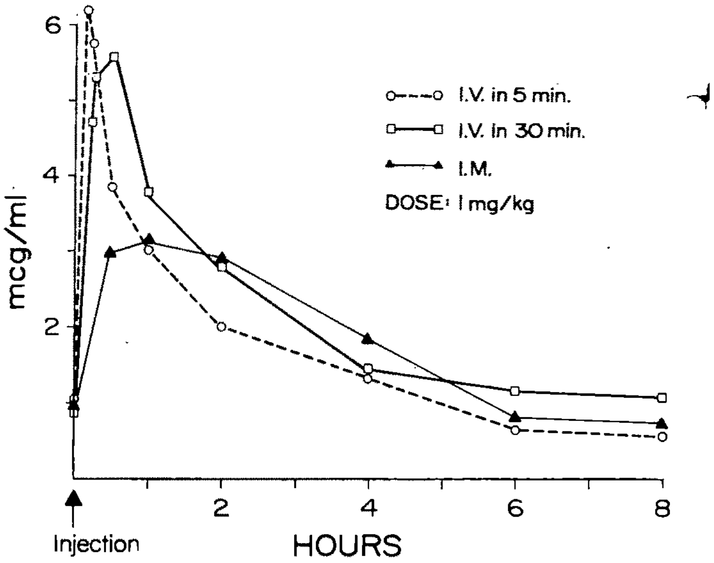

FIG. 3. Serum levels of sisomicin after various routes of parenteral administration.

0.9 mcg/ml at 6 hours, and 0.2 mcg/ml at 12 hours. Values obtained for Amikacin were approximately four times these. As expected, the greater the dose given as expressed in mg/kg of body weight, the higher the peak serum level became and the longer the antibiotic could be detected in circulating blood (Fig. 2). The intravenous route gave much higher and more immediate blood concentrations, although serum levels at 6 and 8 hours were not significantly different regardless of the mode of administration (Fig. 3).

The renal mechanism for aminoglycoside excretion was reaffirmed in all cases. An average of 67% of administered antibiotic could be recovered in the urine at 6 hours; 86%, by 12 hours (Fig. 4). This dependence on normal renal function was well exemplified by the inverse relationship of serum creatinine to rapidity of antibiotic excretion (Fig. 5). In patients whose serum creatinine was 4 mg% or higher, the serum level of aminoglycoside noted at 6 hours was consistently greater than the peak

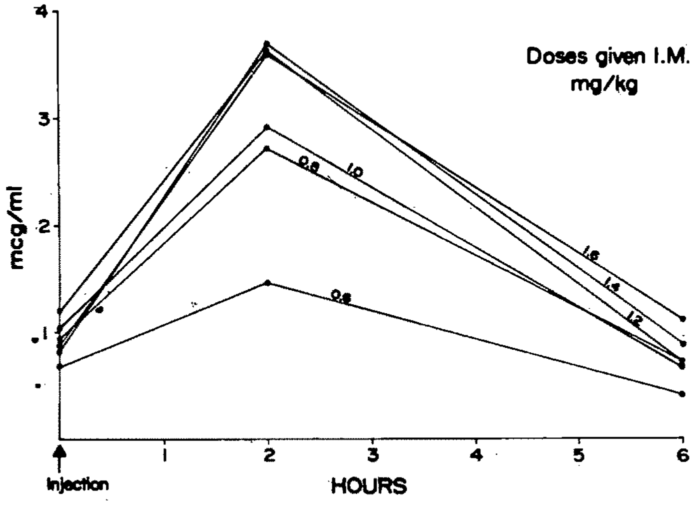

FIG. 2. Serum levels of aminoglycoside following graded doses of sisomicin given intramuscularly.

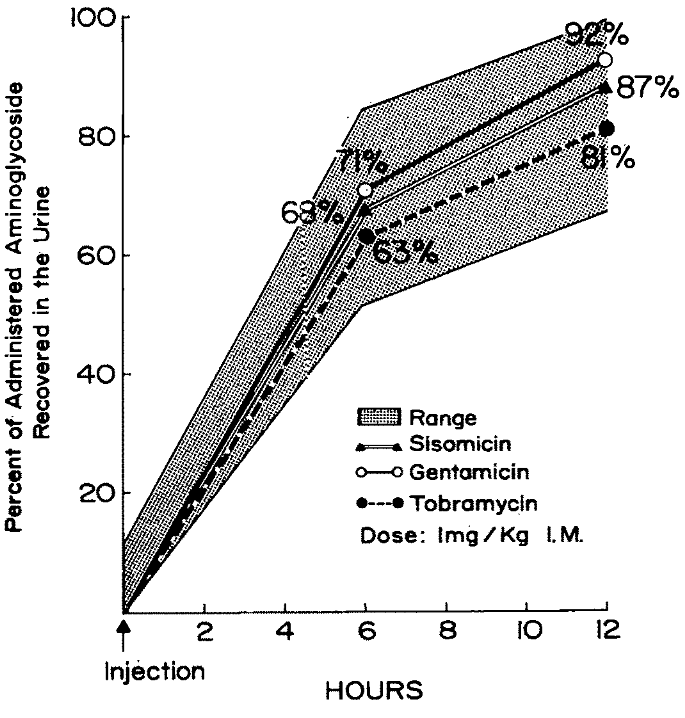

FIG. 4. Per cent of aminoglycoside recoverable from the urine after intramuscular injections at a dose of 1mg/kg body weight.

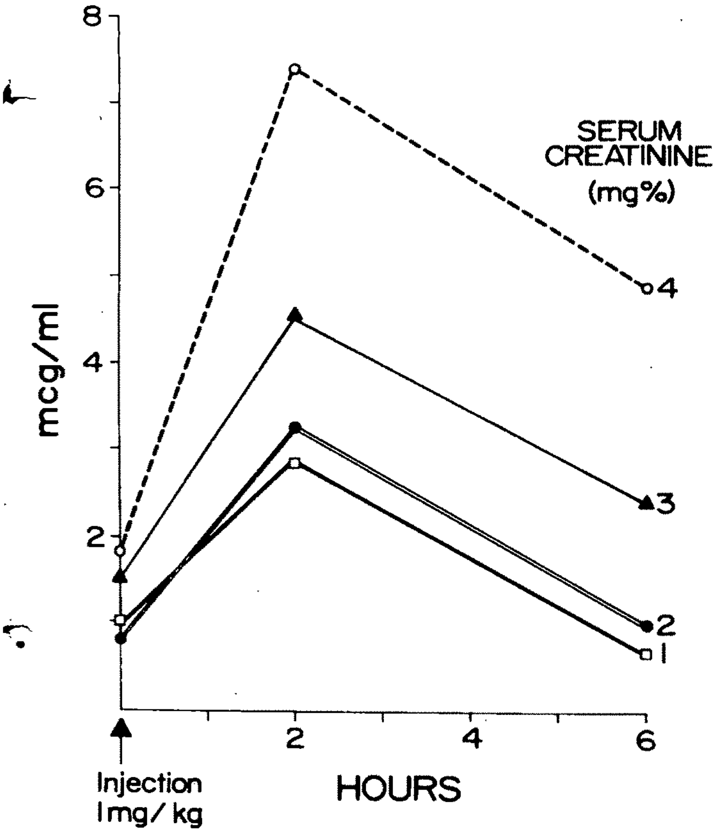

FIG. 5. Serum levels of sisomicin noted after an intramuscular injection (at 1 mg/kg body weight) in patients with varying renal functions as exhibited by individual serum creatinine concentrations.

blood concentration achieved at 1 and 2 hours with a similarly administered dose of the antibiotic in individuals with relatively normal renal function.

Bacteriology

Almost 75% of the 530 aerobic bacterial isolates were gram-negative rods (Tables 3 and 4). *E. coli* represented approximately half of these. Nevertheless, one or more anaerobic species could be grown from the principle site of infection in almost 88% of the cases. Indeed, a polymicrobial flora was generally the rule rather than the exception.

Sensitivity testing demonstrated no significant difference between any of the new study antibiotics, i.e., Tobramycin, Sisomicin, and Amikacin (Tables 3 and 4). This was true for both disc and tube dilution methods. Somewhat lower minimal inhibitory concentrations for those agents with less exposure to hospital pathogens was generally noted on comparing their action to that of gentamicin. Kanamycin and Cephalophin were definitely inferior antibiotics in regard to most gram-negative rods, although the cephalosporin was essentially equivalent to the study aminoglycosides on testing against *Staphylococcus aureus*.

Outcome

Survival of the patient was considerably dependent upon the seriousness of the infection. As categorized

TABLE 3. *Disc Sensitivities of Bacterial Isolates*

	Number of Isolates	Per cent of Isolates Sensitive					
		Tobramycin (10 mcg)	Gentamicin (10 mcg)	Sisomicin (10 mcg)	Amikacin (10 mcg)	Kanamycin (30 mcg)	Cephalothin (30 mcg)
E.coli	206	99	99	100	96	87	63
Kleb-Enterobacter	73	99	100	100	93	91	38
Ps. aeruginosa	61	97	95	99	84	0	0
Proteus sp.	52	92	92	92	87	87	58
Misc. gram-negative rods	33	97	97	97	94	88	64
Enterococcus	67	16	85	25	6	—	16
Staph. aureus	32	97	100	100	94	—	100
Streptococcus	6	17	17	17	17	—	100

TABLE 4. *Tube Dilution Sensitivities of Bacterial Isolates*

	Number of Isolates	Average Minimal Inhibitory Concentration (mcg/ml)					
		Tobramycin	Gentamicin	Sisomicin	Amikacin	Kanamycin	Cephalothin
E. coli	206	3.94	3.61	2.73	11.27	13.48	17.72
Kleb-Enterobacter	73	3.01	2.37	1.37	9.05	9.75	17.95
Ps. aeruginosa	61	.77	2.87	.43	3.87	42.54	48.33
Proteus sp.	52	8.22	6.36	4.29	17.94	18.76	15.42
Misc. gram-negative rods	33	8.25	5.56	5.58	9.69	17.82	35.48
Enterococcus	67	34.28	17.01	26.50	31.81	—	20.88
Staph. aureus	32	1.06	.06	.06	1.96	—	1.09
Streptococcus	6	22.50	31.25	16.25	12.05	—	.10

TABLE 5. *Response According to Identified Pathogens*

	Number of Patients	Bacterial Sepsis		Died of Bacterial Sepsis	Complicating Candida Sepsis
		Cured	Recurred		
E. coli	37	35	1	1	—
Kleb-Enterobacter	13	11	—	2	—
Ps. aeruginosa	26	14	2	1	9
Proteus sp.	15	12	2	1	—
Mixed gram-negatives	62	51	5	4	2
Staph. aureus	12	2	—	—	—
Streptococcus	3	3	—	—	—
Enterococcus	5	5	—	—	—
Anaerobes	17	14	1	2	—
Mixed (aerobes & anaerobes)	176	149	13	11	3
No growth	21	21	—	—	—
No culture	8	8	—	—	—
Indeterminate	10	—	—	—	—
Totals	405	335	24	22	14

by temperature, magnitude of leukocytosis, and presence of shock, septic patients considered to be critical had a mortality of 25%, while those judged to have only mild or moderately serious infections had fatality rates of 2%. The overall mortality rate for the entire series was 10.1%.

Significantly poorer results to antibiotic therapy were noted in patients with extra-abdominal sepsis, that is, in cases of burn and other wound infections and in patients with gram-negative pneumonia (Table 1). In addition, failure to respond to treatment with antibiotics was more likely in those patients given amikacin than when therapy was based upon one of the other study aminoglycosides (Table 2). Refractory infections were more commonly those caused by a mixture of gram-negative rods, especially when such pathogens were acting in symbiosis with anaerobic species (Table 5). Complicating the analysis of these results was the apparently increased incidence of Candida sepsis[5,7] in cases of burn wound infection, intra-abdominal abscess, fungemia following treatment with Tobramycin, and when the infecting bacterium was *Pseudomonas aeruginosa* (Tables 1, 2, and 5). Such conclusions were spurious, however, as they were drawn from data obtained from patients treated earlier in the study and thus before the routine administration of oral nystatin prophylaxis.

Cause of Death

Continuing or recurrent bacterial sepsis accounted for 21 of the 41 deaths. Nine other fatalities were unrelated to the initial infection. Ten deaths, however, were due directly to a complicating candidiasis. As noted above, appropriate prophylaxis with oral nystatin essentially eliminated the occurrence of this one problem in the later cases.[5]

Antibiotic Complications

Forty-three instances of antibiotic related complications developed in 30 of the 405 patients (Table 6). Varying degrees of nephrotoxicity were the most common of these complications. Such was noted in 22 or 5% of the total series, although pre-existing shock and/or severe dehydration appeared to be the primary cause for the renal failure in 16 of the cases. A pure drug-induced effect could be incriminated in only 6 of the patients.

Ototoxicity developed in 6 patients, an overall incidence of just over 1%. In 3 of the patients, it affected

TABLE 6. *Complications of Parenteral Aminoglycosides*

	Tobramycin	Gentamicin	Sisomicin	Amikacin	Total
Renal Toxicity					
drug alone	2	2	1	1	6
with shock/dehydration	6	5	3	2	16
Ototoxicity					
cochlear	1	2	—	1	4
vestibular	2	1	—	—	3
New Pathogen					
Candida Sepsis	8	3	1	2	14
Indeterminate	4	2	2	2	10
No Complication	111	96	109	49	365
Total Patients	129	107	114	55	405

TABLE 7. *Response of Sepsis to Drainage (Drainage inclusive of debridement, as warranted)*

	Number of Patients	Bacterial Sepsis		Died of Bacterial Sepsis	Complicating Candida Sepsis*
		Cured	Recurred		
Already draining	49	35	2	2	8
Spontaneous drain	92	83	2	2	1
Operative drainage	136	122	3	4	5
Never drained**	118	93	17	14	—
Indeterminate	10	—	—	—	—
Totals	405	335	24	22	14

* Candida sepsis developed almost solely in patients with extensive thermal burns or intestinal fistulas.

** Significantly increased rates in mortality and recurrence of bacterial sepsis ($P = 0.01$) for both).

the cochlear division; a vestibular injury occurred in two; while both components of the eighth cranial nerve showed damage in the sixth patient. In each instance, some additional factor seemed to play a major role in causing the inner ear derangement. Specifically, a significant reduction in renal function and thus antibiotic excretion was noted in 5 patients; neomycin had been applied topically and thereby absorbed in four; and prolonged aminoglycoside therapy had been given to two.

There was recovery from the renal injury in all patients who survived, yet kidney failure significantly contributed toward death in the remainder. By contrast, no measureable improvement could be detected in eighth nerve function in any of the patients who demonstrated ototoxicity. No instances of myoneural blockade causing respiratory arrest were noted.

Candida sepsis was an extremely serious complication and was itself the basic cause for death in 10 of the 14 patients who acquired this superinfection. The majority of these cases were noted earlier in the study and led to a frightening 8% incidence of Candida sepsis. Following appropriate prophylaxis, once it was realized that intestinal persorption was the usual portal for entry of such fungi,[5] the frequency of this one complication was reduced dramatically—to less than 1%.

Determinants of Response to Therapy

Drainage of the surgical infection was exceedingly important, irrespective as to whether the area was discharging pus prior to the initiation of antibiotic therapy or subsequently drained through either spontaneous rupture of the abscess or purposeful surgical incision (Table 7). The establishment of such drainage favorably influenced the likelihood of permanent cure, decreased the risk of death from the primary infection, and lessened chances of recurrence of sepsis as well.

Susceptibility of responsible pathogens to the individual antibiotic administered was also important (Table 8). For example, if the bacterial flora was universally resistant to the antimicrobial given, the mortality for such cases was 9%; and the rate for recurrence of sepsis, 11%. If, however, all species of identifiable pathogens were susceptible to the administered antibiotic, comparable rates were 5% for the mortality and 4% for infection recrudescence.

Just as critical to eventual survival, if not even more so, was the presence of a disease state that caused an impairment in host resistance. Comparison of the outcome for those 149 patients with an altered immune response to the results obtained in the 246 individuals presumed to have a relatively normal resistance mechanism reflected a striking difference, that is, mortalities of 19 and 2% respectively, due to sepsis. Even after exclusion of patients dying from Candida sepsis, the difference was still highly significant ($P = 0.01$).

When the relative importance of these three aspects of surgical infections were compared—drainage of the septic process, pathogen susceptibility to the administered antibiotic, and competence of the host defense

TABLE 8. *Importance of Bacterial Susceptibility to Aminoglycoside*

	Number of Patients	Bacterial Sepsis		Died of Bacterial Sepsis	Complicating Candida Sepsis
		Cured	Recurred		
All isolated pathogens resistant	47	36	5	4	2
Only one isolated pathogen sensitive	197	166	14	12	5
All isolated pathogens sensitive	122	104	5	6	7
No growth/no culture	29	29	—	—	—
Indeterminate	10	—	—	—	—
Totals	405	335	24	22	14

mechanism—the value of antibiotic therapy was the least impressive of all. The chances for altering the course of a surgical infection by treatment with an antimicrobial was significant at a probability of only P = 0.10, while the significance for benefit by drainage and an effective host defense mechanism was at the 0.01 level.

Comment

Infections due solely to aerobic gram-negative rods consistently respond to parenteral aminoglycoside therapy whenever the area of sepsis has a good blood supply, all species of pathogenic bacteria are sensitive to the administered antibiotic, host defense mechanisms are routinely normal, and the amount of necrotic tissue is negligible.[7] Drainage of the infection can usually overcome any significant deficiencies in the above, that is, antibiotic-resistant bacteria, accumulation of necrotic debris, and an altered immune response. Thus, the major role of antibiotic therapy often becomes the mere control of sepsis until drainage and/or surgical debridement can be achieved.

Why patients with infections due to a mixed bacterial flora—including aminoglycoside-resistant anaerobes—respond to such antibiotic therapy has been poorly understood. However, these symbiotic bacterial relationships are based upon the anaerobe providing enzymes for tissue digestion and thus nutrient assimilation for all participating species, while the aerobes maintain a lowered oxidation-reduction potential through use of all available oxygen. Each set of partners is thereby supported by the other. Although aerobic gram-negative rods can survive alone, the anaerobes are totally dependent upon the immediate proximity of necrotic tissue or locally available aerobic species.[6] Accordingly, elimination or a significant reduction in the population of the aerobic component will lead to death of most of the anaerobes provided that the volume of necrotic tissue is not great. This may well be the true explanation for an apparent benefit gained from antibiotics lacking activity against anaerobic bacteria.

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DISCUSSION

DR. BOYD W. HAYNES, JR. (Richmond, Virginia): The Bard Parker is still the best treatment for abdominal sepsis, where pus is present; that pus is thoroughly drained is still laudable. However, he was a little surprising to me when he stated that the antibiotic sensitivity of the given organisms doesn't seem to be as important as many of us think.

In our experience, the treatment of gram negative infections, particularly on the burn wound, is often difficult to manage, because, although there is a relatively high sensitivity to gentamicin, and it certainly is the best agent available now to treat that particular spectrum of gram negative organisms, there appears to be a group of pseudomonads now appearing on our wounds which don't seem to be as sensitive as they were previously. This is of some concern to me, and I would like Dr. Stone's comment about this, and also if he thinks that the addition of carbenicillin adds a significant method of control to gram negative sepsis of this type.

DR. H. HARLAN STONE (Closing discussion): The greater importance of host resistance and drainage over antibiotic susceptibility was somewhat amazing to us. If the infection was already draining, antibiotics were effective in determining and controlling which bacteria colonized the wound and thereby would subsequently invade. However, if drainage was accomplished by operation or developed spontaneously, the correlation of antibiotic sensitivities and clinical effectiveness was poor.

I agree with Dr. Haynes' comment that, should there be established drainage, and yet sepsis is still a problem, then antibiotics become quite useful in controlling bacteremia until local wound care can reverse the process. Nevertheless, it is crucial that the antibiotic reach the primary site of infection. For example, parenteral agents for burn wound sepsis fail to work anywhere near as well as do the various topical antimicrobials.

A Prospective Study to Determine the Efficacy of Antibiotics in Acute Pancreatitis

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This study is a double "blind" prospective evaluation of the efficacy of antibiotics (Ampicillin) in the treatment of acute alcohol-induced and idiopathic pancreatitis. Fifty-eight patients with acute pancreatitis were randomly divided into antibiotic and non-antibiotic treatment groups. The two groups were comparable clinically at the onset of the study and other than for antibiotics received identical therapy. The patients without antibiotics had a clinical course equal or slightly more favorable than the antibiotic treatment group in all parameters examined. These data indicate that prophylactic use of Ampicillin is not indicated in patients with routine acute alcohol-induced or idiopathic pancreatitis. The role of prophylactic antibiotics in patients with pancreatitis related to biliary calculi and those with more severe varieties of acute hemorrhagic or necrotizing pancreatitis remains to be more clearly defined.

THE EFFICACY of prophylactic antibiotics in acute pancreatitis has long been a point of controversy. Many authorities have advocated their use routinely.[2,3,-6,7,14,15] while others have condemned this practice.[1,11] A few investigators have stressed the need for a prospective study.[7,11,12] This paper is the result of a double blind, randomized, prospective study designed to evaluate the efficacy of prophylactic antibiotic treatment in patients with acute alcoholic or acute idiopathic pancreatitis.

Patient Selection

All patients admitted to the Nashville Metropolitan General Hospital between January 1971 and December 1973, who had acute abdominal pain diagnosed clinically as acute pancreatitis and confirmed by a serum amylase value greater than 160 Somogyi units per 100 ml, were included in the study.

Patients were excluded from the study according to a previously established protocol if they manifested: 1) history of blunt abdominal trauma; 2) previous history compatible with cholelithiasis or choledocholithiasis; 3) medications: steroids, thorazine, thiaziole diuretics; 4) parathyroid disease; 5) duodenal peptic ulcer disease; 6) a source of fever, independent of the pancreatitis, ancillary antibiotic coverage (i.e. aspiration pneumonia, cellulitis, urinary tract infection, phlebitis, etc.).

Protocol

All patients were admitted to the surgical service and a careful history and physical examination were performed. The following laboratory data were obtained on each patient included in the study: 1) complete blood count, urinalysis, standard chest and abdominal x-rays on admission; 2) amylase, bilirubin and white blood count daily; 3) 24-hr urinary amylase on admission and every 48 hrs; 4) serum electrolytes, blood urea nitrogen, and liver "function" tests on admission and when indicated by the clinical course; 5) serum calcium on admission and after serum amylase had returned to normal; 6) lipid profile on admission (in 37 patients); 7) upper GI series and oral cholecystogram two days

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TABLE 1. *Comparative Profile of 58 Patients Studied*

	Antibiotics	No Antibiotics
No. Patients	31	27
Average Age	34.6 yr (19–58 yr)	36.9 yr (15–87 yr)
Sex	Males 19 Females 12	Males 15 Females 12
Race	Negro 14 Caucasian 17	Negro 17 Caucasian 10
Febrile on Admission: (Rectal temperature above 37.7°C)	15/31 (48%)	12/27 (44%)
Average Serum Amylase:* (Somogyi units) (Normal <160)	770 (177–6000)	780 (184–8680)
Average WBC:* (1000/cc)	10.4 (6.2–23.9)	10.6 (4.6–13.3)
Average Calcium:* (mg%)	9.4 (8.3–10.7)	9.5 (7.5–10.6)
Average Total Bilirubin:* (mg%)	1.5 (0.4–4.8)	1.2 (0.5–2.5)

* Values on admission to hospital.

following the first normal amylase value; 8) urine, sputum and blood cultures on admission and as indicated.

All patients were treated as follows: 1) nothing by mouth; 2) nasogastric suction until return of intestinal peristalsis and return of serum amylase value to normal; 3) intravenous fluids: *Maintenance*: 1500 cc 5% Dextrose with ¼ normal saline per square meter per 24 hr. *Replacement*: gastric output to be replaced cc per cc with 5% Dextrose with ½ normal saline with supplemental KCl added. This fluid regimen was modified as clinically indicated by the usual guidelines of fever, pulse, blood pressure, urinary output, and urine specific gravity. 4) anticholinergics: Atropine 0.4 mg intramuscularly every 6 hr unless specifically contraindicated in patients with glaucoma, prostatism or cardiac arrhythmias; 5) Meperidine (Demerol) for pain; 6) Chlordiazepoxide hydrochloride (Librium) 25–50 mg intramuscularly four times per day; 7) Thiamine 100 mg intramuscularly once on admission; 8) no aspirin, Tylenol or other antipyretics.

Antibiotics

On a randomized pre-selected basis a card was drawn to determine in which group (antibiotic treatment or non-antibiotic treatment) the patient was to be included. The antibiotic chosen was Ampicillin, or in the occasion of penicillin sensitivity, Keflin (1 gram every 6 hrs for 7 days) was used. This occurred in only one patient. In 19 patients the Ampicillin dose was 500 mg every 6 hrs, and in 11 patients, 1 gm every 6 hrs. The average duration of antibiotic treatment was 7 days. Generally by the fourth or fifth hospital day the patients were off intravenous fluids and on oral feedings and oral antibiotics.

Evaluations

All clinical evaluations were made by the senior resident and the chief of the surgical service who did *not* know if the patient had been selected for the non-antibiotic or the antibiotic treatment group. When any indication for surgical exploration occurred, the patient was immediately removed from the study group. This occurred only once, in a patient who was receiving antibiotics.

Patient Profile

During the 24-month study period, 62 patients were admitted to the protocol. Four patient were retrospectively excluded from analysis of the final results.

The two patients from the antibiotic treatment group who were excluded were: 1) a 63-year-old Caucasian man who signed out of the hospital against medical advice after less than two days, and 2) a 69-year-old Caucasian woman who was explored surgically because of persistent fever, jaundice, and failure to improve. She was found to have common bile duct stones.

In the non-antibiotic treatment group two patients were removed for the following reasons: 1) a 29-year-old Negro man who developed signs and symptoms of pneumonia and previously undiagnosed diabetes mellitus, and 2) a 69-year-old man who at autopsy a few months later was found to have metastatic carcinoma of the pancreas.

Fifty-eight patients remained in the study protocol for final analysis. The antibiotic treated group had 31 patients, and the non-antibiotic treatment group had 27.

Results

Table 1 provides a comparative profile of the patients admitted to these two treatment groups. The two groups (antibiotic versus non-antibiotic) are comparable with no statistically significant difference in any category as determined by the Chi square method of analysis.

Lipid profiles were obtained on 37 of the 58 patients admitted to the study. Table 2 outlines these results. There was no important difference in the two treatment groups. The lipid profile was normal in 30 patients. Type V hyperlipemia was not found in any patient.

TABLE 2. *Lipid Profile*

	Antibiotic	Non-antibiotic
Normal Phenotype	14	16
Type III	1	0
Type IV	1	2
"Borderline" Type IV	1	2
Total	17	20

TABLE 3. *Etiology of Acute Pancreatitis in 58 Patients*

	Antibiotic	Non-antibiotic
Alcohol	22	16
Cholelithiasis	1	2
Cholecystitis with Septated Gallbladder	1	0
Undetermined	7	9
Total	31	27

Despite rigorous attempts to limit the study group on admission to patients with acute alcoholic pancreatitis or acute idiopathic pancreatitis, four patients were ultimately proven to have either definite cholelithiasis or anatomical abnormality of the gallbladder. In all instances these diagnoses were first shown by the oral cholecystogram and ultimately confirmed at operation. Table 3 outlines the etiology of the acute pancreatitis in the 58 patients studied.

The results of the contrast radiographic studies performed in 39 patients are listed in Table 4. In the 8 patients in group I-C who had a non-visualized gallbladder following a double dose contrast study, two were subsequently restudied 5 to 8 weeks after their acute episode. Both of these patients had a normally visualized oral cholecystogram when it was not performed during the acute episode of pancreatitis. The other 6 patients refused to have a repeat followup cholecystogram.

The antibiotic treatment and the non-antibiotic treatment groups were compared by the following parameters: Length of hospitalization, number of days required to return to a normal serum amylase value, number of days required for the patient to become afebrile, complication rate, and recurrence rate. Table 5 lists these results. No statistically significant difference was found in any of the parameters except in the recurrence rate. Recurrence was defined as a subsequent attack of acute pancreatitis, requiring hospitalization, which could have been related to many other factors, such as alcohol consumption.

The one death which occurred in the 58 patients studied was in a 45-year-old Caucasian man, a chronic alcoholic who was admitted to the study and randomly assigned to the antibiotic treatment group. On the third hospital day he became progressively disoriented and belligerent. His serum amylase value was 848 on admission and on the fourth hospital day this value had risen to 1200 and his abdomen was moderately distended but non-tender. He was moved to the Surgical Intensive Care Unit where, despite a functioning nasogastric tube, he vomited and aspirated. He was intubated and subsequently had a tracheostomy. He was on a respirator for ventilatory support for 7 days before ultimately succumbing to the effects of hypoxia. No autopsy was authorized by his family. The cause of death was though to be aspiration pneumonia.

Discussion

Several factors need to be analyzed in any attempt to determine the usefulness of antibiotics in a specific clinical situation. First, is the antibiotic chosen appropriate for its assigned task? The antibiotic that we selected (Ampicillin) has bacterial activity against most gram-positive and some gram-negative pathogens. This antibiotic also can achieve good concentration in bile and blood by both intravenous or oral administration.[9] Ampicillin has been recommended for acute pancreatitis by several authors,[2,8] and has been used recently in a similar prospective study by Howes, Zuidema, and Cameron.[10] Second, one needs to consider whether the two treatment groups are reasonably comparable to show meaningful differences in the two treatment regimens. Table 1 indicates that the two groups compared were indeed quite similar as to sex, race, and age, and that the clinical severity of pancreatitis in the two groups on admission was similar as judged by the

TABLE 4. *Contrast X-ray Studies*

	Antibiotic	Non-antibiotic	Total
I. Oral Cholecystogram			
A. Normal study	8	12	20 (51%)
B. Non-visualization on first dose (double dose not performed)	1	1	2 (4.5%)
C. Non-visualization on double dose	6	2	8 (25%)
D. Normal on double dose	3	3	6 (13%)
E. Stones	1	2	3 (6.5%)
			39
II. Upper GI Series			
A. Normal	15	13	28 (80%)
B. "C-Loop" deformity	3	3	6 (17%)
C. Retrogastric mass-pseudocyst	1	0	1 (3%)
			35

TABLE 5. *Results*

	Antibiotic Treatment	Non-antibiotic Treatment
No. Patients	31	27
Total Days Hospitalized (Average)	10.4	11.3
Range	(3–8)	(3–29)
Normal Serum Amylase by Day	5.0	4.5
Range	(2–11)	(2–13)
Afebrile by Day	7.2	5.7
Range	(3–14)	(1–11)
Recurrent Pancreatitis	6 (19.4%)	2 (7.4%)
Complications (Total Patients)	6 (19.3%)	5 (18.4%)
Alcoholic gastritis	1	1
Delirium tremens	3	4
Pseudocyst	1	0
Deaths	1	0

(There is no statistically significant difference in these categories ($P > 0.05$), except for recurrent pancreatitis which could be related to other factors than antibiotic coverage).

temperature, average white blood cell count, serum amylase, calcium, and bilirubin.

Although we attempted to study only those patients with acute alcoholic or acute idiopathic pancreatitis, 4 of our patients (6.9%) eventually turned out to have cholelithiasis or cholecystitis. Our patient population had only one death in 58 cases (less than 2%) which is lower than most reported series (6–25%).[6,13] Our patients also had no septic complications in either treatment group which is less than the only other prospective study reported.[10] On the other hand, our patients may have had a more severe pancreatitis than the patients reported in the Johns Hopkins series as judged by death rate (1/58 versus 0/95), amylase value on admission (770/780 versus 392/365), average number of days required to reach a normal serum amylase value (5/4.5 versus 2/2) and the average number of hospital days required to become afebrile (7.2/5.7 versus 3/3). The duration of hospitalization was comparable in the two studies (10.4/11.3 versus 9/12).

Previous retrospective reports have made conflicting suggestions as to the role of antibiotics in acute pancreatitis. Evans[5] concluded that the use of antibiotics can reduce the incidence of pancreatic abscess from 9 to 3%. Kodesch and DuPont[11] have reviewed 100 patients with acute pancreatitis and their data would indicate no significant difference in the incidence of septic complications in the two treatment groups. The conclusions of this double "blind" randomized prospective study would concur with those of the Johns Hopkins analysis.[10] We found no significant differences in the parameters compared, except in the incidence of recurrent pancreatitis which was actually higher in the antibiotic treatment group. We observed no allergic reaction in our treatment group. However, the theoretical possibility of drug sensitivity and development of resistant bacterial strains, plus the failure to demonstrate any significant advantage with antibiotics suggests that their prophylactic routine use is unjustified.

It should be emphasized, however, that this conclusion applies only to the subset of patients studied here, those with alcohol-involved or idiopathic pancreatitis. Broad spectrum antibiotics or several specific antibiotics may still be indicated in the more severe cases of pancreatitis, such as acute hemorrhagic or necrotizing pancreatitis. The major problem, however, is early identification and separation of this form of pancreatitis from the milder varieties. Patients with pancreatitis related to biliary tract stones likewise may require antibiotic coverage. The assessment of the possible value of the antibiotics in these situations would require another study.

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Discussion

Dr. John Cameron (Baltimore): Over the past 20 years, we have treated acute pancreatitis with what has seemed to be a very reasonable and rational regimen. However, over the past several years various prospective randomized studies have cast doubt upon the efficacy of antibiotics, atropine, and even nasogastric suction for acute pancreatitis.

(Slide) For the past two or three years, over a two-year period, we carried out a study in Baltimore that was very similar to that presented today by Dr. Sawyers. Over a two-year period, all patients presenting at the Johns Hopkins Hospital with a clinical diagnosis of acute pancreatitis, and with a serum amylase level of over 160 Caraway units, were included in the study. All patients with even history numbers were placed on ampicillin, and those with odd history numbers were given no antibiotics.

(Slide) During this two-year periods, 104 patients presented to Hopkins with acute pancreatitis. Nine of these patients were excluded because of physician noncompliance. Forty-eight were placed on ampicillin; 47 received no antibiotics. All received appropriate i.v. fluids, nasogastric suction, Demerol, and atropine.

(Slide) When the various parameters were analyzed, days of amylase elevation, days of fever, days of hospitalization, deaths, septic complications, there were no statistically significant differences in either group: therefore our study agreed with Dr. Sawyers' study. There were eleven septic complications in our 100 patients, five in the antibiotic group, six in the no-antibiotic group.

(Slide) This shows, I think, one of the most interesting aspects of the study. The five septic complications occurring in the antibiotic group included two pancreatic abscesses and three instances of pneumonia. No organisms were obtained on cultures in three of these septic complications, and in the other two, in which organisms were cultured, both were resistant to ampicillin.

On the other hand, in the four instances of pneumonia, one of the unexplained bacteremia, and one pancreatic abscess, in the nonantibiotic group—in five of the six instances the organism was sensitive to ampicillin. So I think that, as in Dr. Sawyers' study, our study showed that antibiotics were of no value, and possibly might even be harmful, by selecting out resistant organisms.

I think this really makes sense, because in most instances of acute pancreatitis it's an acute, sterile, nonbacterial, inflammatory disease thats self-limited, and one really wouldn't expect prophylactic antibiotics to influence the course. However, I think it's important that studies that are prospective and randomized, such as Dr. Sawyers', be performed, to convince us all of that fact.

When a patient comes in with acute hemorrhagic pancreatitis, does he start antibiotics? And if so, does he use ampicillin? Because ampicillin really does not cover the majority of organisms that usually cause pancreatic abscesses. Or does he resort to an aminoglycoside?

Finally, I wonder how many patients he excluded from his protocol who initially presented with fever. In almost every series of acute pancreatitis, there is an incidence of septic complications in the range of 10–15%, with about one quarter or one third being pancreatic abscesses. He had no septic complications in his series, and I wonder if, by excluding patients who were febrile on admission, did he exclude some patients who subsequently went on and did develop septic complications and/or pancreatic abscesses?

Dr. W. Tyree Finch (Closing discussion): I think that earlier, yesterday morning, Dr. Eddie D. Palmer was quoted in support of one of the papers we heard. I'd like to read a very brief portion of an editorial that he submitted to the *Journal of the American Medical Association* last July.

"Acute pancreatitis is a particularly interesting disease on the ward, and a most difficult one to handle in an investigational setting. Assessment of the precise usefulness of any one of the several therapeutic moves ordinarily employed for the management of the acute stage becomes very difficult."

We would certainly agree, and we are glad that the conclusions of our series basically agree with the conclusions of Drs. Howes, Cameron, and Zuidema.

We congratulate them on their paper. I would like to answer Dr. Cameron first.

If you will review carefully the paper when it is printed you will note that we excluded no patients who had fever on admission. There were 31 patients who were in the antibiotic treatment group, 15 of the 31 had fever on admission. Fourteen of the 27 in the nonantibiotic group presented with fever on admission. Our protocol did specify the exclusion of those patients who had fever on admission with an obvious source other than the pancreatitis—cellulitis, pneumonia, any other condition which would require an antibiotic coverage. We had none of that category.

Regarding his question about acute hemorrhagic pancreatitis; I don't believe that we know how to identify on admission, either by the serum amylase or the patient's presentation, the variety of pancreatitis which will go on to subsequently become acute hemorrhagic or acute necrotizing pancreatitis. Our initial protocol stated that if patients in either group failed to improve by serial examinations (by examiners who were unaware of whether the patient was in the antibiotic or nonantibiotic regimen) that they should be removed from the study, and whatever was appropriate, whether broad spectrum antibiotics or surgical exploration, would be performed.

Probably the best use of prophylactic antibiotics, if there is a use, would be to prevent pancreatic abscesses. We know that most of the flora of pancreatic abscesses are those bacteria that are found in the gastrointestinal tract, particularly in the colon—we would assume then that appropriate coverage would have to cover all of the gram negative organisms in the colon, the Bacteroides and Clostridia, and Strep. This would require gentamicin and penicillin, and for Bacteroides, either clindamycin, linkomycin, or chloramphenicol. After hearing Dr. Stone's presentation, I think you would agree, unless you have definite evidence of septicemia, that the routine coverage of this sort would not be indicated in pancreatitis.

Diagnosis and Management of Blunt Abdominal Trauma

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The records of 437 patients with blunt abdominal trauma admitted to Charity Hospital, New Orleans, from 1967–1973 have been reviewed and computer-analyzed. There was an 80% increase in the incidence of blunt abdominal trauma when compared with the preceding 15-year experience. Forty-three per cent of all the patients presented with no specific complaint or sign of injury. Blunt abdominal injury was usually diagnosed preoperatively using conventional methods including history, physical examination, and routine laboratory tests and x-rays. Abdominal paracentesis via a Potter needle had an 86% accuracy. The incidence and management of specific organ injuries with associated morbidity and mortality have been discussed. Mortality and morbidity continue to be significant in blunt abdominal trauma. Isolated abdominal injuries rarely (5%) resulted in death, even though abdominal injuries accounted for 41% of all deaths. Associated injuries, especially head injury, greatly increased the risk. The insidious nature of blunt abdominal injury is borne out by the fact that more than one-third of the "asymptomatic" patients had an abdominal organ injured. A high index of suspicion and an adequate observation period therefore are mandatory for proper care of patients subjected to blunt trauma.

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BLUNT ABDOMINAL TRAUMA (BAT) is seen with increasing frequency in emergency rooms and continues to be associated with significant morbidity and mortality in spite of its improved recognition, diagnosis, and management. Since 1951, almost a thousand patients with BAT have been treated at Charity Hospital, New Orleans (CHNO)—almost half of these since 1967. Our 22-year experience has been reviewed to establish patterns of injury and to assess the results of management. On the basis of this experience it is possible to describe the most accurate and efficient means to establish a diagnosis, the diagnostic and operative procedures with the best results, and the associated morbidity and mortality. Specific questions which have been asked include: 1) What was the major indication for operation in each case? 2) Did delays in getting the patient to the operating room affect the outcome? and 3) To what was death attributable in fatal cases? All cases of BAT treated since 1966 at CHNO were studied and information from each chart was tabulated for computer analysis.

Clinical Material

During the 15-year period from January 1, 1951 through December 31, 1966, 518 patients were treated for BAT at CHNO. These patients have been reported previously by DiVincenti et al.[4] and will not be included in the present review except for purposes of comparison.

In the 7 years from January 1, 1967, through December 31, 1973, the general surgery service treated 437 patients for BAT at CHNO—almost twice the frequency experienced during the preceding 15-year period. This review did not include a substantial number of patients with "renal contusion," since these patients were admitted and managed by the urology service and usually did not present a significant diagnostic or therapeutic problem.

The 305 males (70%) and 132 females (30%) ranged from infancy to 85 years of age (Fig. 1). Seventy-six per cent of the patients were less than 45 years old; 22% were in the pediatric age group. Automobile accidents accounted for 70% of the injuries: 215 passengers and 90 pedestrians with 62% of the pedestrians being in the pediatric age group. Blows to the abdomen (17%) and falls (6%) were the next most frequent causes of BAT. Motorcycle accidents were not a significant etiologic factor among this patient population.

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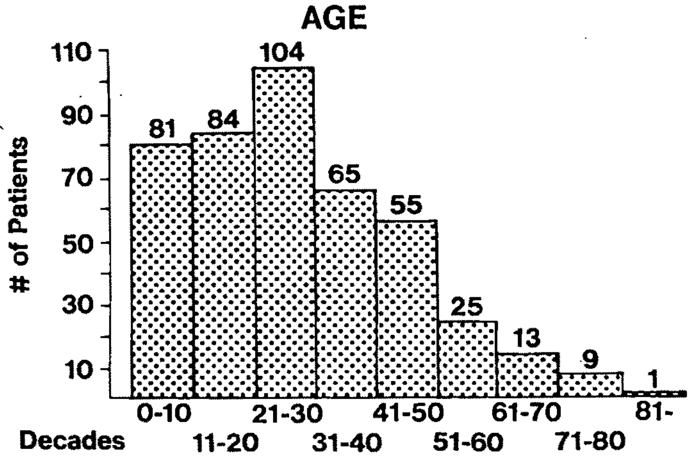

FIG. 1. Age distribution of 437 patients with blunt abdominal trauma.

Clinical Presentation

Generalized abdominal tenderness and abdominal guarding were the most frequent physical findings, both signs being present in more than 75% of all patients. Rebound tenderness and abdominal rigidity were present in 28% of patients. Twelve per cent of the patients were in hypovolemic shock on admission.

Rectal examination rarely gave abnormal findings such as pain or blood (3%). Both rectal examination and nasogastric aspiration should be performed on any patient suspected of intra-abdominal injury, since even negative results aid in diagnosis.

One hundred and ninety (43%) of the total patient population had no specific complaints and no signs or symptoms of intra-abdominal injury when they were first seen in the emergency room. Nevertheless, 84 (44%) eventually required exploratory laparotomy, and 64 (34%) had an intra-abdominal injury. This emphasizes the importance of careful and continuing observation of individuals with BAT.

Diagnostic Procedures

Diagnostic procedures included laboratory tests, x-ray examination, and abdominal paracentesis.

Only 28 patients had a hematocrit less then 30% on admission. Grossly bloodly urine was present in 71 patients (16%), and an additional 88 (20%) had microhematuria.

One hundred-eight patients (25%) had abnormal findings on routine chest x-ray, including 42 (9.6%) with rib fractures, 44 (10%) with hemothorax, pneumothorax, or both; and 9 (2%) with an elevated diaphragm or with abdominal viscera in the chest cavity. Mediastinal widening was seen in only one patient, and none had mediastinal shift.

Routine films of the abdomen were abnormal in 49 (21%) patients. Abnormal findings included free intraperitoneal air in 13 (6%) patients, absent psoas shadows in 10 (4%) patients, and ileus, or dilatation of bowel in 12 (6%) patients. Findings reported by other but not noted in this series include evidence of free fluid, absent or abnormal renal shadows, retroperitoneal emphysema, and displacement of normal gas patterns.

In patients presenting with hematuria and in most of those patients suspected of having injury near or involving the genitourinary tract, intravenous pyelograms were obtained. Cystograms were obtained in some of these patients and in virtually all who had hematuria with accompanying pelvic fractures. The IVP was abnormal in 34 (22%) patients. Cystography was abnormal in 15 patients (14%).

Abdominal paracentesis using the Potter needle was performed in 192 patients (44%). Correct results (positive or negative), as determined by subsequent laparotomy, were obtained in 86%.

Associated Injuries

Associated extra-abdominal injuries were encountered frequently (Table 1). These tend to increase morbidity and mortality directly, and indirectly by distracting attention from the abdominal injury.

One hundred-twenty (27%) of the 437 patients had blunt chest trauma. Thirty-seven patients required either tube thoracostomy or operative thoracotomy. Ten died (4 of 6 requiring thoracotomy, and 6 of 31 requiring chest tube insertion), a mortality rate of 27% in patients requiring both abdominal and thoracic procedures.

Fifty-one patients (11%) sustained an associated extremity fracture, 15 (3%) sustained pelvic fractures, and

TABLE 1. *Associated Injuries and Operations*

Injury	Number	Operation in Addition to Laparotomy	Postoperative Mortality	Death Attributable to Abdominal Injury.
Head	41	6	83%	20%
Thoracic	120	37	27%	40%
Orthopedic	69	26	19%	20%
Combinations	28	8	25%	0%
Total	258	77	29%	27%

TABLE 2. *Associated Head Injury*

	Number	Deaths	Per cent Mortality
Closed head injury	14	5	36
Skull fracture	17	9	53
Closed injury, fracture (Comatose)	10	7	70
Total	41	21	51

three patients sustained vertebral fractures. Another 28 (6%) had combinations of associated injuries.

Of the 41 patients who sustained a serious head injury in addition to BAT (Table 2), 51% died. The head injury was directly responsible for death in 4/5 of these patients, and the abdominal injury was responsible for death in the remaining 1/5. Seven of 10 patients who were comatose on admission died, a figure comparable to that reported by DiVincenti et al.[4]

Management of Specific Injuries

The spleen was the organ injured most frequently (Table 3), almost ⅔ of the injuries occurring as an isolated intra-abdominal organ injury (Table 4). The overall mortality was 20% for patients with blunt splenic trauma. When the spleen was the only abdominal organ injured, the mortality dropped to 3%.

All patients with splenic injury had splenectomy. Approximately ⅓ had drains placed in the left subphrenic space. Drains have been avoided if the splenic bed is dry and the gastrointestinal tract is intact.[2] The mortality figures for splenic injury compare closely with those of Naylor et al.[12] The 20% mortality is an improvement ($P < 0.001$) from the 28% reported by DiVincenti et al.[4]

The liver sustained the second greatest number of injuries, slightly more than half as an isolated injury. Blunt liver trauma has always been associated with a high morbidity and mortality rate. In spite of improved operative methods for managing the traumatized liver,[17,22] postoperative complications occurred in 40% of our patients. The overall mortality rate of 29% for patients with liver injuries is similar to other reports,[10,17,22] but is a marked improvement over the 49% mortality reported by DiVincenti et al.[4]

Only 7 duodenal injuries were recognized during the 7-year study period. There was a 50% postoperative complication rate and one death. The single death was the result of sepsis directly related to the abdominal injury. Blunt duodenal trauma rarely occurs as an isolated injury, and this in part accounts for a continuing mortality rate of 20–26% and a high morbidity rate.[1,3,19] Retroperitoneal duodenal injury may be overlooked because of associated intra-abdominal injury.[3] The surgical approach to duodenal injuries should include debridement, primary repair, and drainage in most patients.

The jejunum or ileum was injured in 34 instances with a 15% overall mortality. No deaths occurred when the jejunum or ileum was the only abdominal organ injured. As noted in other reports,[14,21] jejunal or ileal trauma was usually located near the points of attachment at the ligament of Treitz and the ileocecal valve. The majority of patients were treated with suture repair, but approximately ⅓ required resection of injured bowel. More than half the survivors of these injuries had postoperative complications directly associated with their abdominal injury.

Kidney and bladder injuries frequently were associated with pelvic fractures and retroperitoneal bleeding. The overall mortality for kidney and bladder injuries was 19%, and was attributable to the associated severe crush injury, multiple organ injuries, and retroperitoneal hemorrhage.

Retroperitoneal bleeding has been approached on a selective basis. Upper abdominal retroperitoneal hematomas above the pelvic brim are explored routinely. Nonexpanding pelvic hematomas in stabilized patients are not opened.[16] In the present report slightly more than

TABLE 3. *Abdominal Organs Injured*

Organ	Total Injured	Died	Per cent
Spleen	108	22	20%
Liver	72	21	29%
Jejunum, Ileum	34	5	15%
Kidney	30	4	13%
Bladder	17	5	29%
Mesentery	15	1	7%
Right colon	10	2	20%
Left colon	10	5	50%
Pancreas	8	3	38%
Duodenum	7	1	14%
Gallbladder	6	5	83%
Diaphragm	6	3	50%
Stomach	6	0	0%

TABLE 4. *Isolated Abdominal Organ Injuries*

Organ (Total Injuries)	Isolated Injuries	Per cent Total	Deaths Attributable to Abdominal Injury
Spleen (108)	67	62%	2 (3%)
Liver (72)	37	51%	5 (14%)
Jejunum, Ileum (34)	15	44%	0
Kidney (30)	15	50%	0
Urinary bladder (17)	12	71%	1 (8%)
Mesentery (15)	8	53%	0
Left colon (10)	4	40%	0
Right colon (10)	3	30%	0
Pancreas (8)	2	25%	0
Gallbladder (6)	1	17%	0
Stomach (6)	1	17%	0
Total (316)	165	53%	8 (5%)

TABLE 5. *Complications*

Type	Number	Per cent Total Patients
Cardiovascular-Pulmonary	126	29%
Intra-abdominal	75	17%
Wound	23	9% of operated cases
Urinary tract	22	5%

105 of 229 postoperative survivors (46%) developed one or more complications.

half were explored and drained. The remainder were left intact. External counterpressure[11] was not utilized during the period under study, but has been employed recently with success in at least two cases.

Twenty patients sustained colon injuries with a mortality rate of 35%. Five of the 7 deaths occurred after left colon injuries. Colon injuries usually occur in association with other abdominal organ injury[8,9] and the mortality rate is related directly to the number of organs injured. Proximal colostomy was the usual method of management of colon injuries.

Of the 8 patients who sustained blunt injury to the pancreas, 3 died, 2 from uncontrolled hemorrhage and one from sepsis. Neither of the 2 patients with isolated pancreatic injury died. Blunt pancreatic injury should be managed by debridement of all nonviable pancreatic tissue coupled with wide drainage, as recommended by Northrup.[13] The significant complication rate previously reported from CHNO by Smith and Drapanas[18] was duplicated in our experience. Only one patient survived without complications.

Morbidity

Of the 229 postoperative survivors, 124 (54%) recovered without a complication. Cardiovascular and pulmonary complications occurred in 29% (Table 5). Intra-abdominal complications included peritonitis, pancreatitis, subphrenic and subhepatic abscess, liver abscess, fistula, delayed postoperative hemorrhage, and intestinal obstruction. Wound infection, progressing to dehiscence in two patients and evisceration in a third, developed in 9%. Urinary tract complications occurred in 22 patients, including 7 who developed varying degrees of renal failure.

Mortality

In addition to the 15 patients who died in the emergency room, 3 (2.6%) died following nonoperative management, and 40 patients died after operation (Table 6). This represents a postoperative mortality of 14.8% and an overall mortality of 13.3%.

Discussion

Forty-three per cent of the patients in this series gave no indication other than history that they had sustained BAT. The subtlety with which organ injury can exist secondary to BAT is exemplified by the figures showing that 84 (44%) of these "asymptomatic" patients were eventually explored and 3 out of 4 had an injury which required repair. Proper management of these patients requires careful initial evaluation followed by a period of observation.[7] Diagnostic procedures should be limited to those examinations that have proven effective in BAT and should not delay laparotomy in an unstable patient. One should not jeopardize the care of a seriously injured patient by obtaining examinations of low yield. Utilization of this time to initiate resuscitative measures and to prepare for abdominal exploration is of much greater benefit to the patient.[6]

The patient who has sustained blunt abdominal trauma may have sustained injury simultaneously to other systems, and it is particularly important to examine for injuries of the head, thorax, and extremities. Care of the injuries in any of these systems may take precedence over the abdominal trauma. Failure to recognize an extra-abdominal injury may contribute to the patient's death, when a relatively simple procedure might otherwise have saved the patient's life. The mortality figures presented here provide evidence of the need for close attention to these other injuries (particularly closed head wounds).

In addition to a rapid and accurate history and physical examination, including rectal examination, and which gives special attention to the other areas of the body

TABLE 6. *Deaths Attributable to Abdominal Injury*

Therapy	Number	Deaths	Deaths Attributable to Abdominal Injury
Died in emergency room	15	15	6
Admitted for observation	153	3	0
Negative laparotomy	40	2	0
Surgery, no repair necessary	30	4	2
Surgery, repair required	199	34	15
Total	437	58 (13.3%)	23 (41%)

TABLE 7. *Early Management of Patients with Blunt Abdominal Trauma*

1. History and physical
2. Intubate: Airway, nasogastric tube, Foley catheter, IV and CVP lines
3. Lab Work: Urinalysis, CBC, amylase, cross-match
4. X-rays: Chest, abdomen, skull, IVP, cystogram, angiogram, extremities (as indicated)
5. Peritoneal aspiration

just mentioned, the initial evaluation should include basic steps listed in Table 7. The chest x-ray will not only call attention to any associated injuries to the chest and mediastinal structures, but should also indicate if there has been a rupture of the diaphragm with the intrathoracic displacement of some of the abdominal viscera. The abdominal films may reveal the presence of air under the diaphragm, evidence of massive retroperitoneal hemorrhage, enlargement of the kidney, enlargement of the splenic shadow, blurring of the psoas shadows or retroperitoneal air, any one of which should hasten surgical intervention. When hematuria is present, IVP can be obtained while the patient is in x-ray. Once x-rays have been obtained, paracentesis or lavage can be performed where indicated. The trauma center providing initial care ought to be capable of providing any of the listed procedures within a few minutes of a patient's admission to the unit.

Abdominal paracentesis, using a Potter needle for either a four-quadrant tap, or a bilateral flank tap proved to be very accurate in assessing the presence of intraperitoneal blood. An abdominal paracentesis was performed on 75 of the 190 patients who originally had no signs or symptoms of injury, and a correct diagnosis was confirmed by subsequent operation in 88%. Paracentesis can be performed rapidly with minimal delay and requires no specialized equipment.[5] If positive, the test is highly reliable. Peritoneal lavage[15,20] provided the correct diagnosis in 4 patients for whom it was used.

The surgeon's justification for operation was apparent in all but 9 of the 269 operated cases. The most common indication for operation (45% of those operated upon) was a positive finding on one or more of the diagnostic procedures already discussed. An additional 105 patients (39%) were explored because of physical findings. Twenty-eight patients (10%) had a laparotomy because of severe hypovolemic shock. The remaining 9 were operated on for miscellaneous reasons. In 95% of the operated cases the managing physician was able to make a preoperative diagnosis using physical findings or one or more of the relatively simple diagnostic procedures described previously. In only 15% was the exploration negative. Only when diagnosis is uncertain are more sophisticated diagnostic methods needed.

The time lapse between injury and induction of anesthesia was calculated for each patient, and physician or patient delays were noted. There was no significant difference in morbidity or mortality in the group of patients whose operation was delayed, regardless of the reason.

The cause of death was attributable to the abdominal injury in 41% of cases. Associated injuries, especially head trauma, were responsible for the remainder of the fatalities. In patients requiring multiple procedures, the abdominal injury was the cause of death in 27% of cases. If only a single abdominal organ was injured, it was infrequently the cause of death.

The overall mortality rate of 13.3% represents an improvement ($P < 0.001$) when compared with the 23% reported by DiVincenti et al. (Table 8). Central venous pressure monitoring, improved methods of prevention and management of post-traumatic respiratory insufficiency, and a decreased incidence of associated head injury during the latest study period undoubtedly accounted for some of the improvement.

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TABLE 8. *Mortality*

	1967–1973			1951–1966 (3)		
	Number	Deaths	Mortality	Number	Deaths	Mortality
Died in emergency room		15			53	
Nonoperative management	153	3	2.0%	106	18	18%
Operated	269	40	14.8%	359	49	14%
Total	437	58	13.3%	518	120	23%

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DISCUSSION

DR. WILLIAM S. MCCUNE (Washington, D.C.): I rise to reemphasize a complication of blunt trauma which is not often included in a discussion of this subject, and that is mesenteric thrombosis. The interesting thing about this particular complication is that it may not be suspected, and can occur from one to two months following the original injury.

(Slide) Our interest in this began several years ago, when a woman came into our office complaining of abdominal pain. It was not very severe. She was a little bit obtunded mentally. She had some abdominal tenderness, not very specific; she might possibly have a little intra-abdominal fluid.

The story is that three weeks previously she had attended a dance, and her partner in the course of the dance threw his arm around her from behind and lifted her, kicking, high in the air.

On the following day she went to see her doctor, who said, "You have a little muscle strain. Don't worry about it", and gave her some medication. But apparently it continued, rather naggingly, and so she came in to see us.

We gave her the usual diagnostic tests, including an upper g.i. series, a gallbladder series, and a barium enema. But finally, not having a diagnosis, we recommended operation.

At surgery she had a gangrenous loop of bowel, which you see depicted in this drawing, about 12 inches below the ligament of Treitz, with thrombosis extending into the mesentery, where it had undoubtedly begun. We resected the bowel, and also the grey area surrounding it, and she did well for about six days, when she again complained of abdominal pain.

(Slide) At operation another area of gangrenous bowel was found separated from the first by several inches. Apparently, in removing the mesentery at the first procedure, we had failed to take it back far enough, so that the thrombosis in the mesentery proceeded out a little farther and involved another loop of bowel, separated from the first.

(Slide) This was resected, and she was given anticoagulants, which we probably should have used at first.

There is a case in the German literature, of a patient who was involved in an altercation in a railway station and thrown against the steps of a train. He had some abdominal trauma, but he got up, vomited a couple of times, and continued on his way.

One month later he developed severe abdominal pain, and was operated upon and found to have extensive mesenteric thrombosis. In the post-mortem following his death, the clot in the mesentery was followed back to a well-organized thrombosis in the ileocolic vein, indicating, apparently, the site of his original injury, with gradual propagation to produce involvement of most of the mesenteric venous system.

We have also found that in inflammatory intraabdominal conditions, the platelet count in the mesenteric blood may be from 1 million to 2 million, as compared with a normal platelet count in the peripheral blood. Thus any trauma, even operative trauma, such as rough packing, and so forth, is more apt to produce mesenteric thrombosis, if there is an inflammatory condition with it.

The main points I want to make are that mesenteric thrombosis following trauma often occurs late, when the patient is apparently recovered; secondly, that enough mesentery must be removed to prevent an extension of the thrombosis to another area.

DR. RICHARD J. FIELD (Centreville, Mississippi): Several years ago, Dr. Raymond Martin and I, who is here today, reviewed 44 cases of retroperitoneal duodenal injury in blunt trauma of the abdomen. I want to take you quickly through three points that we thought were very important in this rare—as there were only seven in Dr. Cohn's group—but very tragic problem.

(Slide) The first point is, as he pointed out, with many of the blunt trauma areas of the abdomen, there are very few symptoms which occur early in this problem. There may be none at all, as I am sure you do know. These are fundamental, simple slides, but I want to remind you of this injury, because it is so terribly dangerous.

(Slide) The next point is how simply it can occur. As you know, the duodenum is essentially a soft-tissue tube which is partially closed at the distal end, by the ligament of Treitz, and the proximal end by the pyloric sphincter, which filled with gas and fluid, thus a very small force can rupture this tube. If you watch football like I do, it's amazing that all running backs don't have retroperitoneal rupture of the duodenum.

(Slide) This slide is simply a diagrammatic description of the hard surfaced vertebra. This portion (indicating) of the duodenum is impinged upon, and six to eight pounds can very easily produce a laceration.

(Slide) The high mortality rate which is frequently found is directly related to how long we wait to operate, which is, of course, directly related, as Dr. Barnett mentioned a while ago, in gangrenous bowel, to the index of suspicion of the surgeon.

Thus our three points are: How easily it can occur, how few symptoms one has with this, and how important the index of suspicion of the surgeon is.

Dr. Jonathan Rhoads spoke of gangrenous bowel as a very vexing problem a few moments ago. I would leave you with the thought that retroperitoneal rupture of the duodenum is a very bewitching problem, and it can only be conquered by a high index of suspicion and prompt action.

Dr. William R. Drucker [Charlottesville, Virginia]: There are at least two excellent experimental studies in the literature in which a patient's blood, introduced into their peritoneum, has been found *not* to produce pain. And yet we know that free blood in the peritoneum may be associated with pain.

The experimental studies may be criticized on a temporal basis. That is, after a period of time will the asymptomatic patient with free blood in the peritoneium eventually begin to experience pain? This clinical study may shed light on that issue.

My question for Dr. Cohn is: What was it in the rather large number of patients that you said came in without abdominal symptoms that finally led you to doing something definitive? Was it the fact that their vital signs changed? Was it response to your peritoneal lavage? Did they eventually develop pain?

Dr. Joe Jack Davis (Closing discussion): Dr. McCune mentioned mesenteric thrombosis. We did not see one case in reviewing our series. I think that probably can be best explained by the fact that most of our patients have already come back with their second case of trauma before we had a chance to recognize mesenteric thrombosis.

In answer to Dr. Drucker's question about what prompted surgery in those patients that we saw who were initially considered to be asymptomatic, it was just what Dr. Cohn stated: They had developed some clinical sign, some complaint, or some eventual finding on one of the diagnostic tests mentioned.

In closing this discussion, I think several points warrant amplification. Blunt traumatic injuries are on the rise, and they seem to be so even with the reduced speed limits and improved motor vehicle safety devices. The associated overall mortality of 13% that we saw demands attention.

Promptness in diagnosis and treatment of these injuries must be our goal.

This study was a review from a large trauma center, which, as already stated, is staffed by residents. And I think it attests to the fact that a relatively unsophisticated, but organized, approach, utilizing basic laboratory and x-ray tests and abdominal paracentesis with a Potter needle, can be successful on the attainment of this goal.

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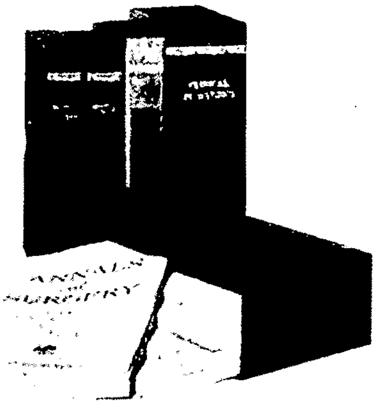

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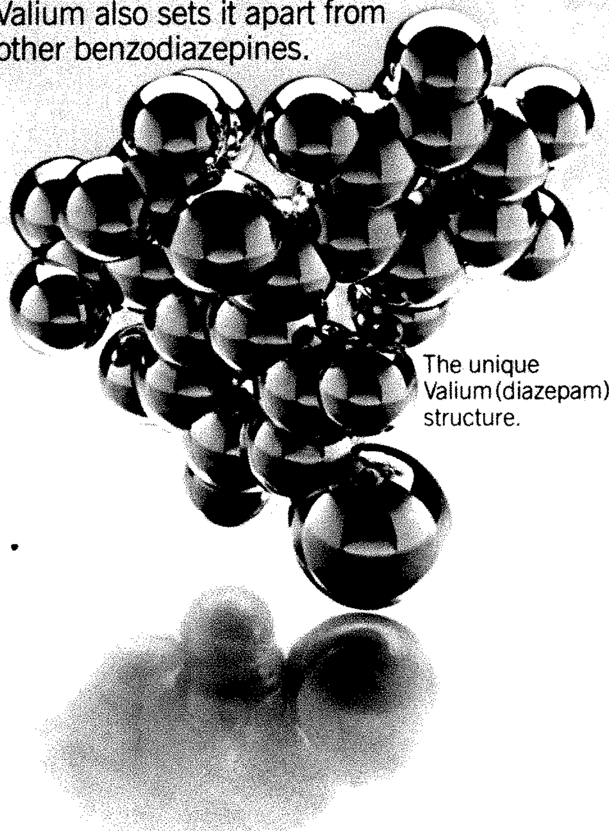

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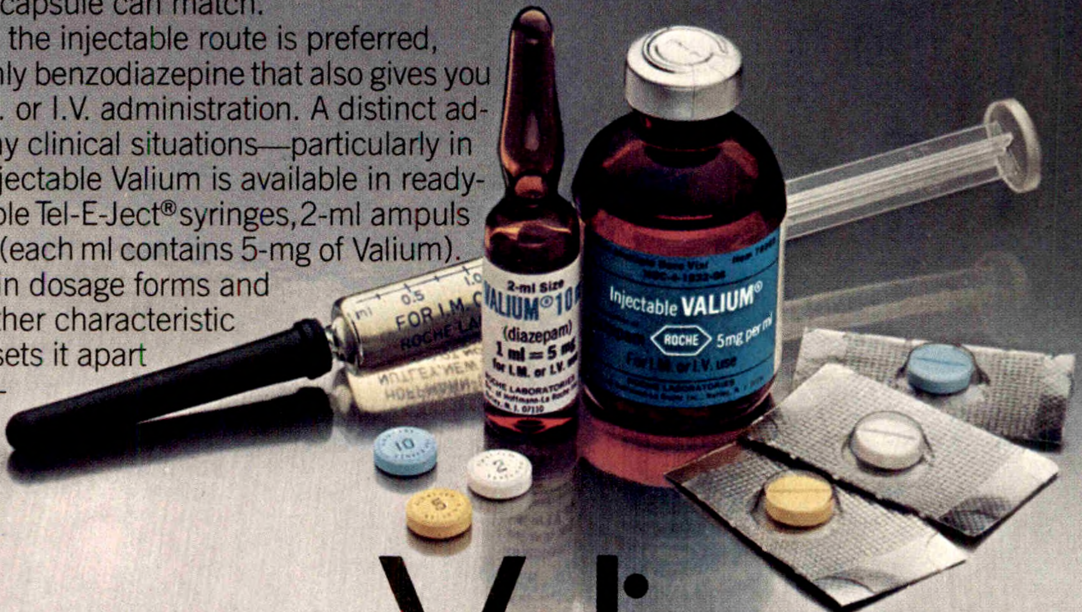

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Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome. *Oral form* may be used adjunctively in convulsive disorders, but not as sole therapy. *Injectable form* may also be used adjunctively in: status epilepticus; severe recurrent seizures; tetanus; anxiety, tension or acute stress reactions prior to endoscopic and surgical procedures; cardioversion.

Contraindications: Use of Injectable in infants and Tablets in children under 6 months of age; known hypersensitivity to drug; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: As with most CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Advise patients against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals (drug addicts or alcoholics) under careful surveillance because of their predisposition to habituation and dependence. Use of any drug in pregnancy, nursing women or in women of childbearing potential requires that expected benefit be weighed against possible hazard.

ORAL: Not of value in treatment of psychotic patients; should not be employed in lieu of appropriate treatment. When using oral form adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may also be associated with temporary increase in frequency and/or severity of seizures.

INJECTABLE: *When used I.V., the following procedures should be undertaken to reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment. Inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; extreme care should be taken to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Administer with extreme care to elderly or very ill and those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; resuscitative facilities should be available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓ and administer in small increments. Not recommended for OB use until additional information is available. Should not be administered to patients in shock, coma or in acute alcoholic intoxication with depression of vital signs.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Limit oral dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed or tolerated).

INJECTABLE: Laryngospasm and increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic and have necessary countermeasures available; hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly and debilitated; safety and efficacy in children under 12 not established.

Adverse Reactions: Side effects most commonly reported were drowsiness, fatigue and ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued.

Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Valium (diazepam) therapy and are of no known significance.

INJECTABLE: Venous thrombosis and phlebitis at injection site, hypoactivity, syncope, bradycardia, cardiovascular collapse, nystagmus, urticaria, hiccups, neutropenia.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat or chest have been reported.

Dosage: Individualized for maximum beneficial effect.

ORAL—*Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg *b.i.d.* to *q.i.d.*; acute alcohol withdrawal, 10 mg *t.i.d.* or *q.i.d.* in first 24 hours, then 5 mg *t.i.d.* or *q.i.d.* as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg *t.i.d.* or *q.i.d.*; adjunctively in convulsive disorders, 2 to 10 mg *b.i.d.* to *q.i.d.* *Geriatric or debilitated patients:* 2 to 2½ mg 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg *t.i.d.* or *q.i.d.* initially, increasing as needed and tolerated (not for use under 6 months).

INJECTABLE: Usual initial adult dose is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.

Moderate psychoneurotic reactions, 2 to 5 mg I.M. or I.V. and severe psychoneurotic reactions, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary; muscle spasm, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); status epilepticus, severe recurrent convulsive seizures, 5 to 10 mg I.M. or I.V. initially, repeat in 2 to 4 hours if necessary. In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V., within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma and diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Immediate gastric lavage indicated for overdosage with tablets. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

Supplied: Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® (unit dose) packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10. Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam, compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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The Healing of Liver Wounds

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Cases of traumatic hemobilia are often characterized by a protracted history with recurrent episodes of hemorrhage over many years. It seems that while the liver regenerates quickly and profusely it heals slowly and poorly. This is in contradistinction to the kidneys where lesions often heal within a short time. In order to investigate the cause of this peculiar behavior a series of experiments was performed where local lesions were produced in the musculature, in the kidneys and in the liver of dogs. The healing process was studied at different intervals. There was essentially no difference between the rate and character of healing in the three localities. As the lesions that produce hemobilia are open to the biliary tract, another series of experiments was performed where the healing took place in presence of bile. The effect of this was striking with a very diminished production of fibrinous exudate, granulating tissue and fibrous scar.

JUDGING FROM the literature,[8] there is a steady increase in the frequency of traumatic hemobilia, i.e., the syndrome of bleeding through the biliary tract after liver injury. Trauma, especially from traffic accidents, is by far the most common cause of hemobilia. Forceful compression of the liver results in disruptive forces which produce tears and cavities in the center of the fragile and non-elastic liver parenchyma. The rupture tears bile ducts and blood vessels, and the cavity fills with bile and blood. Such central liver ruptures seem to be as frequent as tears through the capsule[1] but do not produce the alarming symptoms caused by bile leakage and hemorrhage into the peritoneal cavity.[6] They might, in fact, heal without any symptoms at all, but will often result in hemobilia with a typical and characteristic clinical picture.

Blood clots lodged in the diverting ducts prevent emptying, and the distension of the cavity will cause enlargement of the liver with discomfort to the patient. The intra-cavity pressure aided by fibrinolysis will one day suddenly force the clot down the biliary tract, this being accompanied by biliary colic and followed by a large gush of blood which manifests itself as hematemesis and/or melena. When the clot is located peripherally it will produce obstructive jaundice. Biliary colic, gastrointestinal bleeding and jaundice make up the classical triad of the hemobilia syndrome.[8]

Traumatic hemobilia has certain characteristics. Frequently there is a significant time interval of weeks and months between the trauma and the onset of symptoms. Another characteristic is a very long duration of years, or even decades with periodic recurrence of symptoms. (A case of a lady with a hemobilia history of 36 years after the liver trauma has been described earlier.[8] She had been treated for chronic secondary anemia and had had cholecystectomy and blind gastric resection before she was finally cured through resection of a large hemobilia cavity diagnosed with the help of hepatic arteriography).

While the liver parenchyma has a powerful regenerating capacity, it is obvious from the protracted course after a central liver rupture that the healing capacity of

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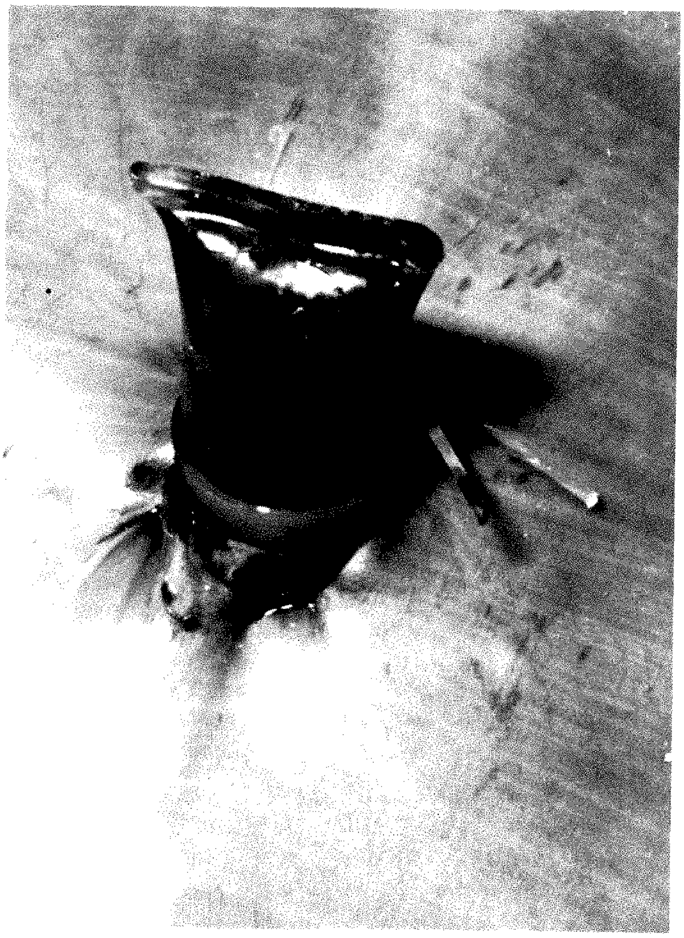

FIG. 1. Polyethylene tube with one end closed introduced into the musculature and fixed to the surface.

local lesions is poor. Thus, paradoxically, the liver regenerates its mass quickly and profusely, but local healing is slow and poor. This is in contra-distinction to the kidneys where lesions generally heal promptly.[5]

Liver regeneration has been the subject of a tremendous number of investigations from all points of view.[4] Local healing which admittedly is of far less theoretical interest has hardly been investigated at all.[2,9] We, therefore, decided to examine and compare the local healing process in the liver, the kidney and the musculature, expecting to confirm the poor local healing in the liver.

Methods

Seven mongrel dogs were used for the experiments. The healing was studied histologically at different time intervals. At laparotomy, under general anesthesia, incisions were made through the capsule of the liver and the kidney and into the abdominal musculature. Polyethylene tubes, 2.5 cm long and 0.75 cm wide with one end closed, were then introduced with the open end embedded in the tissue and fixed in position (Fig. 1). This produced a raw circular surface of parenchyma at the bottom without direct contact with the tube, where the healing process could be studied (Figs. 2 and 3). These tubes do not cause foreign body reaction.[7] At intervals of one week, 3 weeks, 3 and 6 months after creation of these lesions the dogs were sacrificed. The part of the organ containing the tubes was excised and fixed in formalin. After fixation the tubes were removed and the lesion cut longitudinally (Fig. 2). Stained histological slices were prepared.

Results and Comments

Examination of the slices demonstrated the typical layers of wound healing, from the bottom: a) fibrous layer; b) granulating layer; and on top, c) fibrinous exudate (Fig. 3). Up to the 3-week stage, there was no difference in the healing process in the 3 locations, either qualitatively or quantitatively. After 3 months, there was some difference in that the scarring was completed in the kidney but still in progress in the liver and in the musculature.

On the whole, the difference in healing could not account for the difference in clinical behavior observed

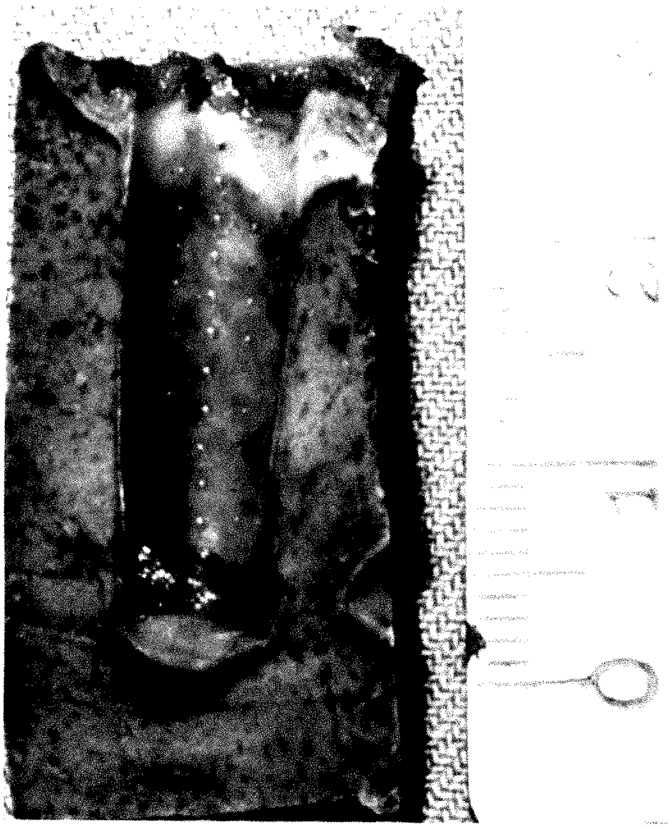

FIG. 2. Portion of liver with lesion, resected and fixed in formalin. The tube has been removed and the lesion cut longitudinally to allow study of healing at the bottom.

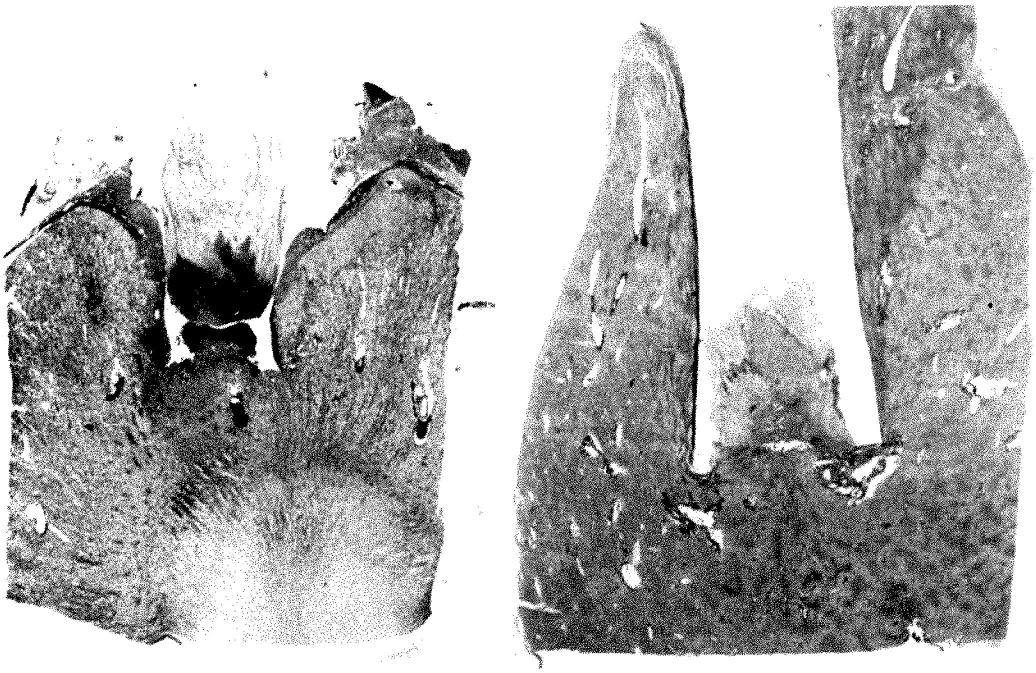

FIG. 3. Three weeks after injury, there is essentially no difference in healing in (left), kidney and (right) liver. Stained histologic sections, natural size, show the three healing layers with the fibrinous exudate on top, the granulating tissue in the middle and the fibrous scar at the bottom.

in patients with hemobilia. We had thus not found support for our previously outlined hypothesis.

However, on further consideration, we realized that the liver wound surface in our experiments had not been submerged in bile as occurs in a hemobilia cavity. In order to achieve such a condition, we performed a second series of experiments on livers of another 9 dogs where one tube was introduced into the parenchyma from the inside of the gallbladder and the other directly from the peritoneal cavity. This time both ends of the tubes were left open (Fig. 4). In these experiments we resected the omentum to prevent it from covering the tubes placed directly through the Glissons Capsule. As in the first series, dogs were sacrificed after time intervals of one week, 3 weeks, 3 and 6 months. The lesions were then prepared as described, studied and compared.

From a quantitative point of view, there was a big difference as all the layers in the wounds that had been submerged in bile were without exception considerably thinner at every time interval (Figs. 5 and 6). By measuring them with a micrometric ocular, the thickness of the fibrous layer was found to be on an average little more than half, the granulation layer one third and the fibrinous exudate only one fifth of those of the wounds that had been open to the peritoneal cavity.

From a qualitative point of view the 3 layers were very similar except that where the tube was open into the gallbladder, the bottom fibrous layer was more dense and less vascular (Fig. 7).

The striking diminution of all 3 layers in liver wounds healing in the presence of bile fully explains the char-

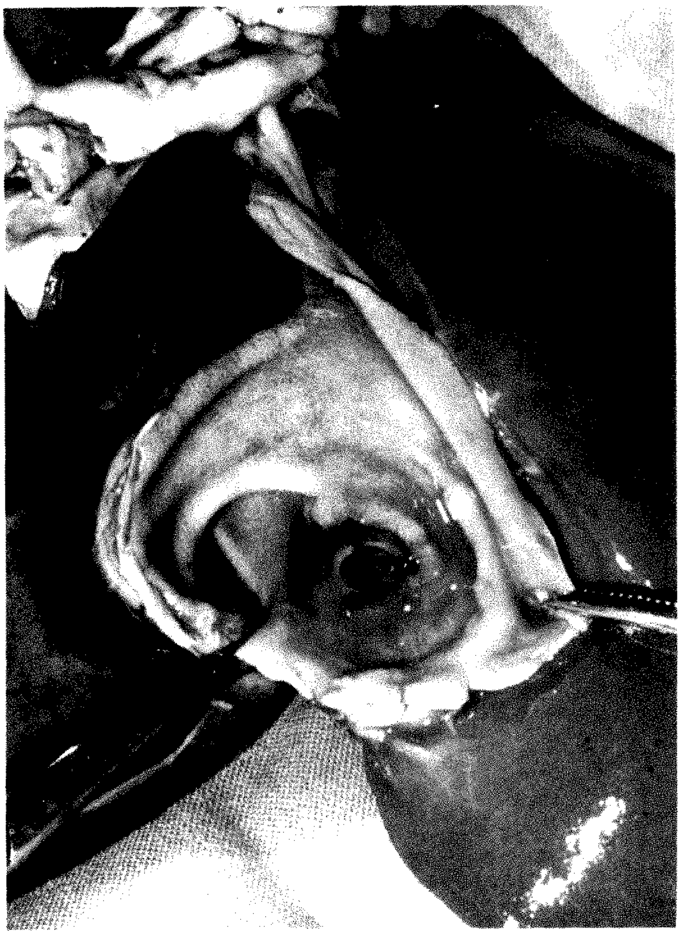

FIG. 4. The tube with both ends open has been introduced into the liver parenchyma from the inside of the gallbladder. This was then closed.

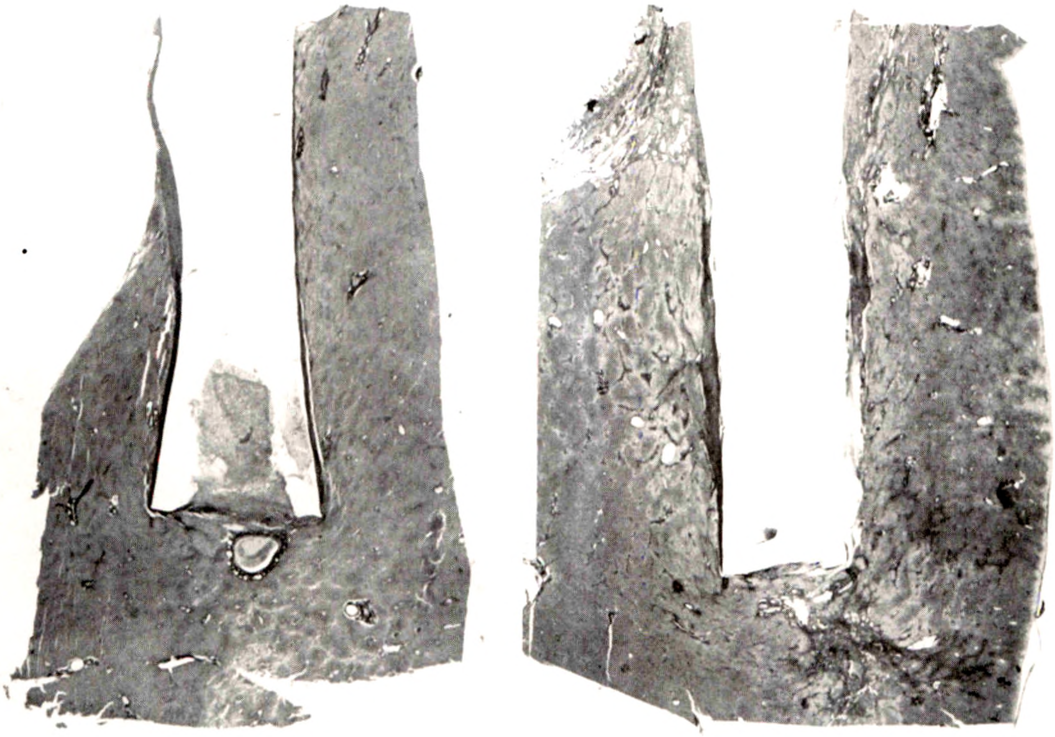

FIG. 5. Three weeks after injury, there is normal healing of the lesion open to the peritoneal cavity (left), but hardly any healing tissue in the lesion open to the gallbladder (right).

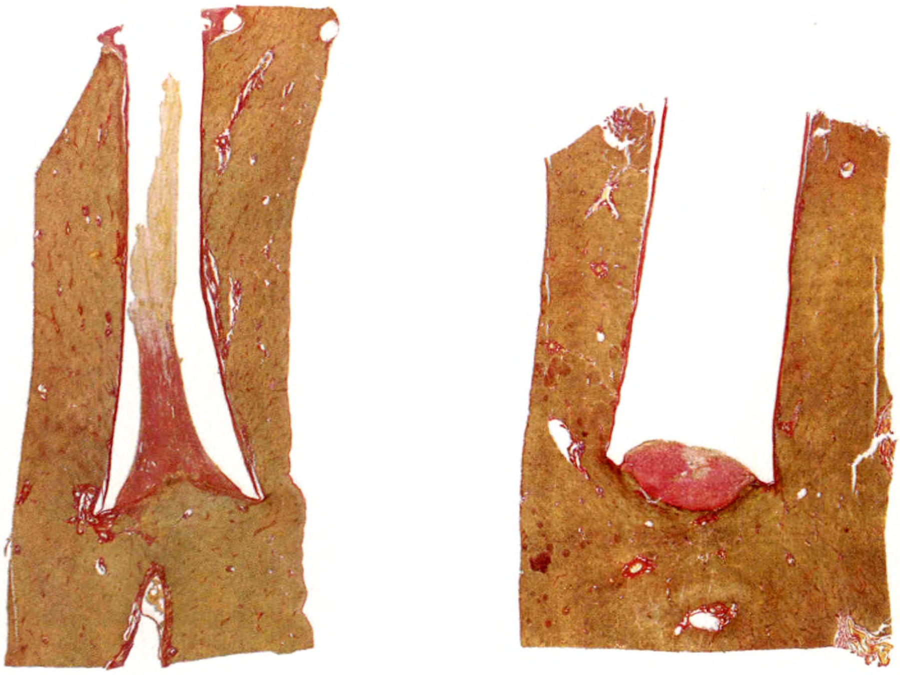

FIG. 6. Three months after injury, the difference in amount of healing tissue is even more marked. The fibrous tissue in the wound bathed with bile is dense with few vessels. (Left) lesion open to peritoneal cavity. (Right) lesion open to gallbladder.

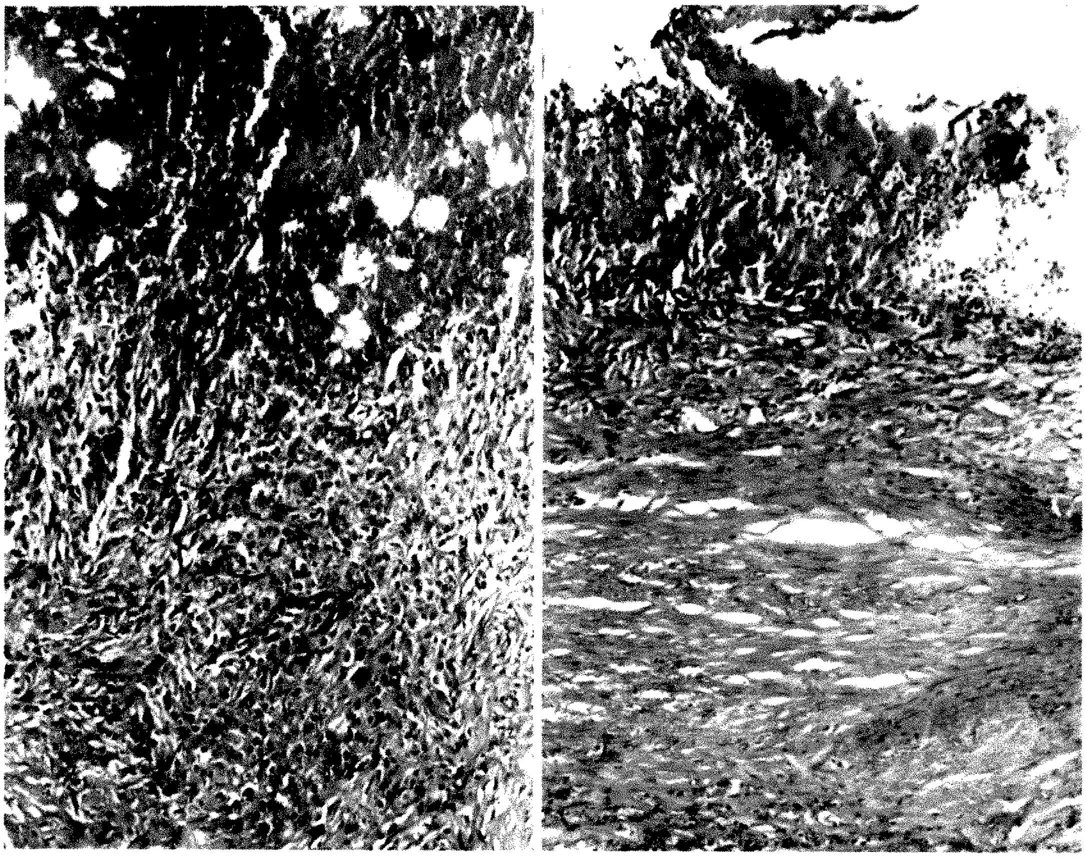

FIG. 7. Histologic sections × 132, 3 weeks after injury demonstrate difference in quantity but not in quality of the 3 wound layers: fibrinous exudate on top, granulating tissue in the middle and fibrous scar at the bottom. (Left) lesion open to peritoneal cavity. (Right) lesion open to gallbladder.

acteristic delay in healing of hemobilia cavities. The question that remains is how the bile acts, whether it is through fibrinolysis or cytotoxicity, a combination of both, or through some other property.

Hinman and Oppenheimer[5] found a similar adverse effect of urine on the healing process in the ureter. When urine flowed constantly through a ureter with an experimental defect, the epithelialization was delayed, the fibrous reaction was great, and smooth muscle regrowth was retarded as compared to the conditions where the urine was diverted from the defect. There is thus a great similarity which is not surprising since urine, as well as bile, has both fibrinolytic and cytotoxic qualities. The generally rapid healing of kidney lesions is probably due to satisfactory drainage of the urine.

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DISCUSSION

DR. PAUL T. DECAMP (New Orleans): We had a case a number of years ago which is been unique in our experience and we hope it remains so. This was a patient who had had a percutaneous liver biopsy done on the medical service, and began to hemorrhage from the gastrointestinal tract. After a number of hours, it became apparent that surgical relief was necessary. This was before the days we were doing angiography routinely in this sort of problem.

We operated on the patient, and the puncture wound in the liver didn't help us very much, except to tell us that the biopsy had been taken from the right lobe of the liver. We opened the common duct and were able to confirm that the blood was coming from the right lobe of the liver. And we were faced with: Did we do a right hepatic lobectomy, or not?

That seemed to be a rather major undertaking for a complication of a percutaneous biopsy, so, with some trepidation, we put Oxycel up the right hepatic duct. We figured that if that didn't work, we could always do a right hepatic lobectomy later.

I am happy to announce that we have not had to do the right hepatic lobectomy.

Dr. J. Philip Sandblom (Closing discussion): Although there is very little risk in doing percutaneous liver puncture, just about every year, there appear three or four papers on patients who bleed after liver puncture, to the extent that they require some surgical procedure.

As Dr. deCamp mentioned, nowadays, with arteriography, we can often find the lesion. Probably the best thing, to do, if it's peripheral, is to do a resection; if it's central, to do ligation.

I saw a case of Dr. Scott's in Vanderbilt where, after arteriography, a local resection could be done.

Naturally, we have continued to work on this problem, and we are going to do biochemical studies of those wounds to see if there is any difference; to see if the kidney wounds perhaps heal worse in the presence of bile, and perhaps also compare the healing in the biliary tract and the urinary tract, when the bile, respectively, and the urine is diverted from the healing point.

Selective Operative Treatment for Tetralogy of Fallot:

Rationale and Results

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Eighty-one patients with tetralogy of Fallot malformations evaluated between July 1, 1971 and November, 1975 are presented. Fifty-one patients underwent primary intracardiac repair; three died. Twenty-seven patients were corrected after a previous palliative shunt; there was one death. Three additional patients have been palliated and are awaiting repair. While the overall mortality in these patients was less than 5%, the infants undergoing total correction before the age of two years appeared to be at greater risk (25%). There were no deaths in the group of patients undergoing palliative procedures. Based on these data it appears that a safely performed palliative shunt in the symptomatic small infant is a reasonable first step, particularly if the outflow tract of the right ventricle is diffusely hypoplastic.

SURGICAL TREATMENT of the tetralogy of Fallot malformation had its origin when Dr. Alfred Blalock[2] performed the first subclavian-pulmonary artery anastomosis for this condition in 1944. During the next decade operative treatment consisted entirely of palliative procedures designed to increase pulmonary blood flow in the cyanotic child with this malformation. In 1955 the intracardiac correction of tetralogy defects became a reality following development of extracorporeal circulation.[5,7] Many of the early corrective procedures were done on small infants but operative mortality in this group was high. For this reason palliative systemic-pulmonary anastomosis as a preliminary procedure before eventual total correction was advocated by many.[10,12,13] During the next two decades uncertainty about the choice and timing of palliative and corrective procedures resulted in many different approaches to the surgical treatment of these children. In recent years, the intracardiac correction of most congenital defects in the small infant has become possible with improvements in surgical techniques. As a result, interest in correction of the tetralogy malformation in the symptomatic infant has been renewed, and there has been a movement toward immediate correction of the tetralogy malformation by most surgeons and cardiologists. Our choice of a palliative or corrective operation has been based primarily on the specific intracardiac anatomy defined by precise angiography. In the past 4 years all patients with the tetralogy malformation, despite age or size, were considered for correction unless the intracardiac anatomy was considered unfavorable for primary correction.

Clinical Material

Eighty-one patients with symptoms of tetralogy of Fallot have been evaluated at the Vanderbilt University Medical Center since July 1, 1971. There were 45 males and 36 females, whose ages ranged from 10 days to 46 years. The selective treatment employed in these 81 patients was based upon consideration of the patient's clinical course and specific intracardiac anatomy.

Fifty-one patients underwent total correction as the first

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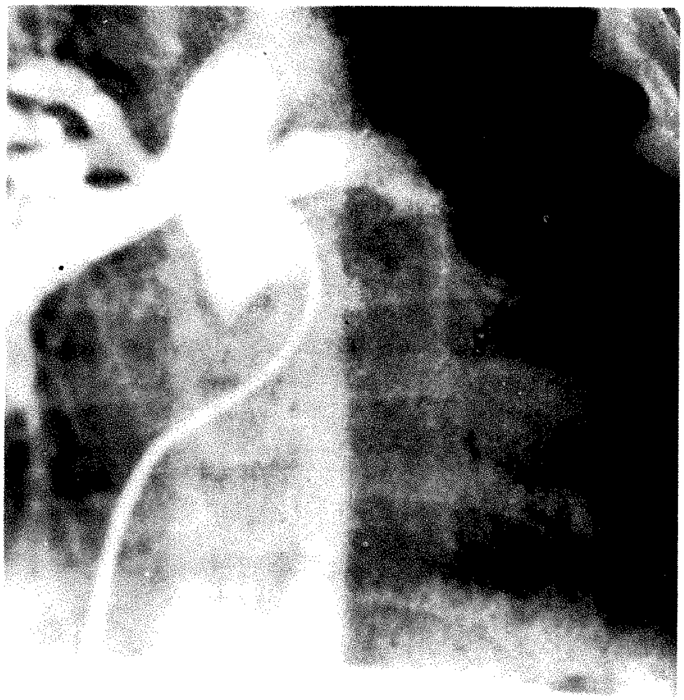

FIG. 1a. Postoperative aortogram in a patient with tetralogy of Fallot after a Waterston anastomosis. Flow into both pulmonary arteries can be detected in the properly positioned posterior aortopulmonary anastomosis.

and immediate procedure after diagnosis because the intracardiac malformation in this group was judged favorable for total correction by the usual criteria.[6] The pulmonary arteries were of satisfactory caliber and the right ventricular outflow tract was not diffusely hypoplastic as determined by subjective assessment of angiocardiograms. Although right ventricular volume measurements were calculated in each, these data added little to the subjective assessment of the adequacy of the right ventricular outflow tract. Body size and weight was of secondary importance in the consideration of immediate total correction in this group. Generally assessment of the technical ease of total correction was the dominant consideration in the selection of total correction for these patients.

In the remaining 27 patients who underwent intracardiac repair, a preliminary systemic-pulmonary anastomosis was performed prior to total correction in each. In 17 of these 27 patients, the selection of the staged approach to total correction was made prior to July 1, 1971 or at another institution. In the other 10 patients we chose to proceed with preliminary systemic-pulmonary anastomosis; in these 10 patients the principal reason for this choice was the configuration of the right ventricular outflow tract. Three additional patients with tetralogy of Fallot were evaluated by the authors and felt to have complex outflow tract anatomy and had shunt procedures as their primary operative procedure. These patients are presently well and awaiting intracardiac repair.

Operative techniques for the creation of the systemic-pulmonary shunts have become relatively standardized. The Blalock-Taussig anastomosis[2] remains our first choice for the palliative shunt and it was performed in 9 of the 13 children and infants. This shunt was always done if the subclavian artery was found to be of sufficient caliber at the time of thoracotomy for the palliative shunt. On the other hand, if the arteriographic findings suggested a diminutive subclavian artery in the small infant, a systemic-pulmonary shunt as originally described by Waterston[15] was used; 4 of the 13 patients underwent preliminary Waterston anastomoses.

Operative Methods

The technical aspects of the total correction as well as the method for creating a systemic-pulmonary anastomosis have been refined by Kirklin,[6] McGoon,[8] Cooley,[3] and others.[1,9,11,14] Several technical refinements and improvements in the overall management of the infant undergoing total correction have proved useful for us in recent years. Intraoperative monitoring is identical for patients undergoing either total correction or palliative shunts except for the placement of an intra-arterial catheter in the children undergoing cardiopulmonary bypass. The operating room is previously

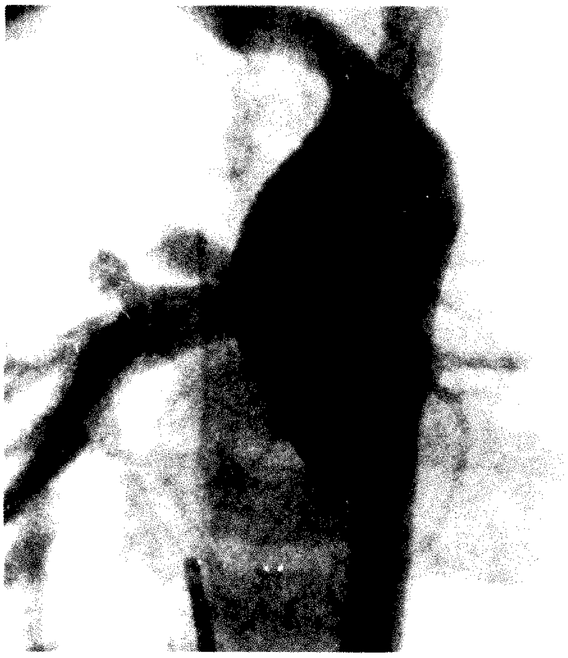

FIG. 1b. Postoperative aortogram in a patient with tetralogy of Fallot after a Waterston anastomosis. Preferential flow to the right pulmonary artery can be identified because of the creation of the anastomosis on the posterolateral aspect of the ascending aorta.

warmed to prevent inadvertent cooling of these infants. Each child lies on a warming blanket throughout the operation. Arterial pressure monitoring is achieved in the small infants undergoing shunt procedures by the use of photoelectric pulse sensors. Continuous temperature and electrocardiographic monitoring is employed in all patients. The conduct of anesthesia is a critical consideration in these infants and two experienced anesthesiologists in constant attendance throughout the procedure can be of extreme importance. The same intraoperative monitoring is continued into the recovery period for patients undergoing shunts or total correction. Assisted or controlled ventilation is provided until it has been demonstrated by arterial blood gas determination that the infant or child can be safely extubated.

The same technical emphasis is given to the palliative operation as to the total corrective procedures. Head lamp illumination and optical magnification have proved valuable for the small anastomoses. For the shunt procedures, a full posterolateral thoracotomy was necessary to provide for excellent exposure for the systemic-pulmonary anastomoses. For the Waterston shunt the right pulmonary artery is exposed posterior to the superior vena cava and dissected free well into the mediastinum. In this manner the anastomosis can be placed on the posterior aspect of the aorta. This posterior placement of the Waterston anastomosis will provide perfusion to both pulmonary arteries and will avoid undesirable kinking of the right pulmonary artery (Figs. 1a and b.) Similarly, for the Blalock-Taussig shunt, the right pulmonary artery is dissected to the main pulmonary artery and the subclavian and innominate artery are mobilized to the aortic arch to avoid undesirable tension and kinking of the anastomosis.

The technique for total correction always consisted of cardiopulmonary bypass with moderate general body hypothermia (30 C). Deep hypothermia and circulatory arrest was not used in the series. A vertical right ventriculotomy was used in all but three patients; in those three patients an anomalous left anterior descending coronary artery arising from the right coronary artery required a transverse ventriculotomy. The standardized techniques of the intracardiac repair including infundibular resection and patch closure of the ventricular septal defect were utilized.

Outflow tract reconstruction by means of fabric or pericardial patches across the pulmonary annulus was required in nearly one half (13/27) of the patients undergoing total correction after a preliminary systemic-pulmonary anastomosis (Fig. 2). This frequency of outflow tract reconstruction in this subgroup of patients reflects the more severe degree of infundibular hypoplasia in those patients selected for a preliminary systemic-pulmonary anastomosis. In contrast, 14 of the 51 patients undergoing primary correction of tetralogy of Fallot required major outflow tract reconstruction.

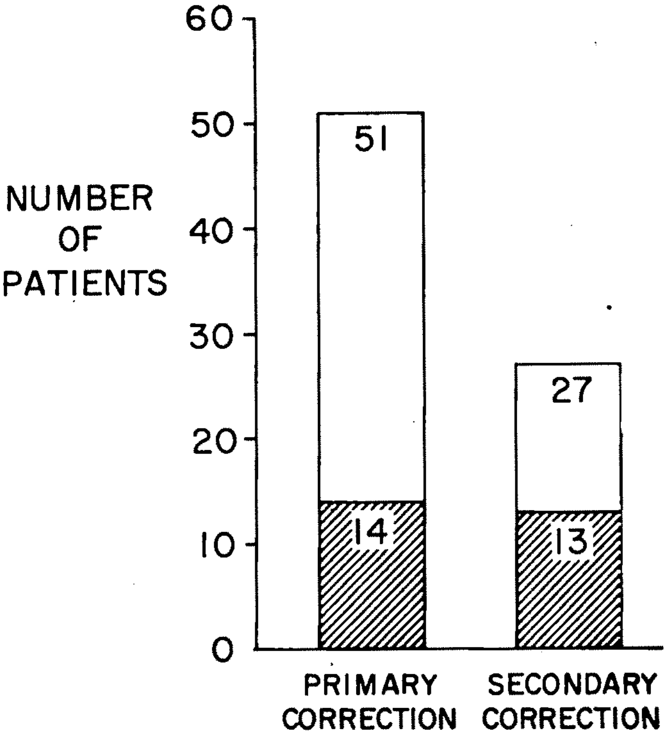

FIG. 2. Graphic comparison of the necessity of outflow tract reconstruction in 51 patients undergoing total correction without a preliminary systemic-pulmonary shunt and in 27 patients undergoing total correction following a systemic-pulmonary shunt. The hatched areas represent these patients requiring outflow tract reconstruction. The severity of the outflow tract malformation is reflected by the greater proportion of patients requiring outflow reconstruction at the time of secondary correction.

Results

In the 13 patients undergoing palliative systemic-pulmonary anastomosis, there have been no deaths. Immediate symptomatic improvement was achieved in all 13 patients.

Total correction has been performed in 10 of these 13 patients; one of these 10 patients was a 14-month-old child who died of disseminated intravascular coagulation in the immediate postoperative period. The other 9 patients are asymptomatic. The 3 patients who have not yet been corrected are symptom-free and total correction is planned. There were no operative deaths in the 17 patients who underwent subsequent total correction after undergoing shunt procedures done before 1971 or at another institution, and each of these patients is now asymptomatic. Thus, of the 27 patients undergoing secondary correction, 26 are living and well (Fig. 3).

Of the 51 patients who underwent primary intracardiac correction of their defects, there were 3 deaths in the

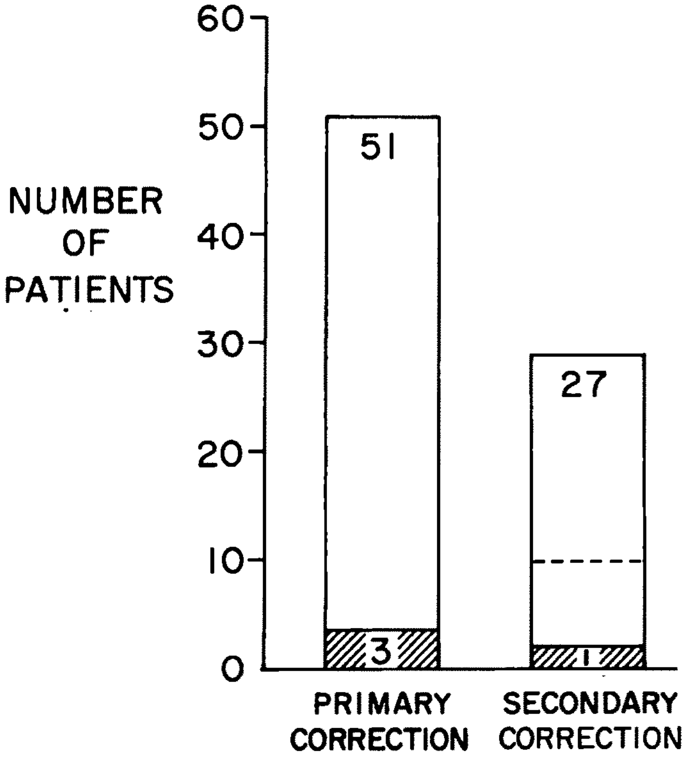

FIG. 3. Graphic comparison of the operative mortality between patients undergoing intracardiac repair of tetralogy of Fallot without previous systemic-pulmonary anastomosis (primary correction) and with a preliminary palliative shunt. There is no significant difference in the mortality experience for the two groups. (chi-square analysis P = 0.46)

postoperative period (Fig. 3). The remaining 48 patients are asymptomatic. The 3 patients who died were among the youngest and smallest infants in this group of 51 patients. Each weighed less than 9 kg and their ages were 2, 10, and 15 months. Two of these 3 deaths resulted from inadequate cardiac output after the procedure and the third resulted from sepsis. Each of the three infants required outflow patch reconstruction.

Twenty-six operations for symptomatic relief of tetralogy of Fallot were performed in 24 patients who were less than two years of age. The distribution of ages is shown in Table 1. The dominant consideration in the choice of palliative or corrective operation for this subset of 24 patients was the subjective assessment of the severity of the right ventricular outflow tract malformation. Fourteen of these 24 patients underwent immediate intracardiac correction while 10 of the patients underwent immediate palliative systemic-pulmonary shunt as the first step in the surgical treatment of tetralogy of Fallot. Two of the 10 patients who underwent immediate palliative shunt procedures subsequently have undergone total correction before 2 years of age. The operative mortality for this subgroup of the youngest patients is depicted in Fig. 4. None of the 10 infants undergoing shunting procedures died as a result of the shunt procedure. Three of the 14 patients undergoing primary total correction died; one of the two patients undergoing total correction after a preliminary shunt died. These 4 deaths were the only deaths among the entire group of 78 patients undergoing total correction.

TABLE 1. *Age Distribution of 24 Patients Less Than Two Years of Age Undergoing Surgical Treatment for the Tetralogy of Fallot*

0– 6 mon	2 patients
7–12 mon	4 patients
13–18 mon	10 patients
19–24 mon	8 patients

Discussion

The selective operative treatment of tetralogy of Fallot has developed from previous surgical failures and surgical successes with the operative management of various subsets of patients with the tetralogy of Fallot. We originally thought that a significantly higher operative mortality might be found in those patients with the most severe intracardiac malformations. It was in this subset of patients with hypoplastic pulmonary arteries and diminutive outflows tracts that we initially considered to be the greatest operative risks for total correction and therefore advised palliative operations as their first operative procedure. When our results were analyzed, it became evident that there was no significant difference in the operative mortality between the subgroups of patients with localized outflow tract obstruction and those with diffuse infundibular obstruction and a small pulmonary annulus. The lack of correlation of operative mortality in these two subsets could likely be explained by the selective approach to their management. In those infants and children with hypoplastic outflow tracts, a temporizing palliative shunt provided time for growth so that total correction proved easier at a later date.

On the other hand, it could be argued that in reality there is no essential difference in the operative mortality in these patients when contrasted on an anatomic basis. Certainly, if an acceptable overall mortality is to be achieved in the patients selected to undergo the two stage approach to total correction, the operative mortality for the palliative operation must be low and there must be no attrition among those patients awaiting total correction. Both these requirements have been satisfied in our group of patients undergoing palliative procedures. We continue to view the palliative systemic-pulmonary shunt as an important surgical adjunct to the total correction of tetralogy of Fallot. Despite the high operative mortality[4,10,11] which has been reported following shunt procedures and used as a reason to advocate immediate total correction in patients with tetralogy of Fallot, we feel that this operation can be performed safely even in the smallest infants with symptomatic tetralogy. For the operative mortality to be acceptably low, the same careful attention to detail must be used as that employed for the total corrective procedure. Similar monitoring and supportive measures are necessary to provide an acceptable low operative risk for the infant undergoing a palliative shunt. Similarly, the operation must be performed or immediately supervised by an experienced cardiac surgeon.

Because there was no difference in the operative mortality when compared on an anatomic basis, we looked further at various subsets within the group of patients undergoing total correction. No correlation could be identified with a previous palliative shunt, with the degree of hypoxemia, with the use of patch reconstruction of the outflow tract, or with severity of preoperative symptoms. However, a definite trend was identified when the analysis was made solely on the basis of body weight and age. It became apparent that the greatest operative risk was age irrespective of the severity of his intracardiac malformation. In the subset of infants less than two years of age the mortality for total correction was 25%. In contrast, no deaths were encountered in the 10 patients undergoing shunt procedures who were less than two years of age; moreover, the severity of the tetralogy malformation was generally greater in this group. In the remaining 62 patients who were two years of age or older, there were no deaths following intracardiac repair regardless of the presence or absence of a systemic pulmonary shunt.

As a result of our continuing reassessment of the surgical results in the treatment of tetralogy of Fallot, we have developed guidelines we are presently using in the selective management of these patients. We select a palliative systemic-pulmonary shunt as the first and immediate form of surgical treatment in the small infants, usually less than 10 kg, who is experiencing symptoms. At the present time we would recommend palliative shunts for virtually all these small symptomatic infants. Even in the larger infant under two years of age whose right ventricular outflow tract is narrowed by more than simple localized infundibular stenosis, we would recommend an initial palliative systemic-pulmonary anastomosis. Furthermore, if complicating anatomic configurations e.g. anomalous coronary circulation, are identified by angiography in the infant, we prefer to delay total correction. In those patients who have undergone an initial palliative procedure, the timing of subsequent total correction should not be unduly delayed. Once reasonable body size has been attained, usually in the immediate preschool years, we recommend total correction. In the rare child who develops recurrent symptoms or signs of arterial hypoxemia with a previous palliative shunt, we recommend total correction. A second palliatve systemic-pulmonary anastomosis in a symptomatic child with tetralogy of Fallot is a poor alternate selection.

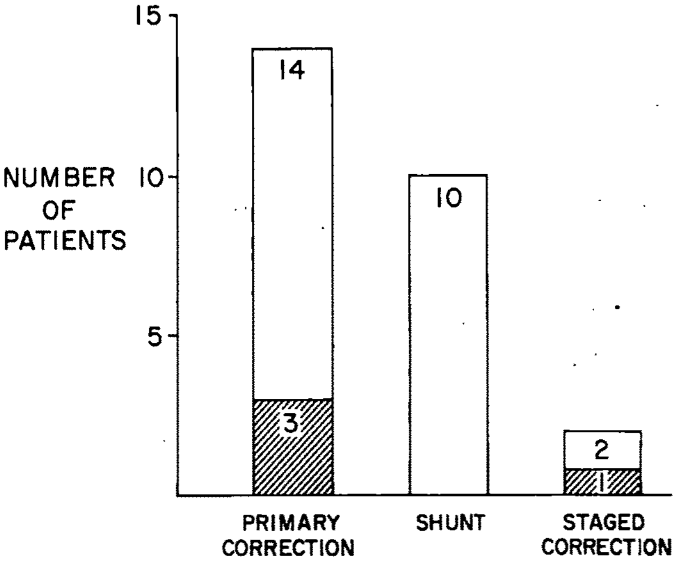

FIG. 4. Graphic representation of the results of surgical treatment of 24 infants under two years of age. Three postoperative deaths (hatched areas) occurred in the 14 patients undergoing total correction without a previous systemic pulmonary shunt. One of the two patients undergoing secondary correction died postoperatively. There were no deaths in the infants undergoing palliative shunts.

Total correction as the primary step is recommended for the majority of patients. Most children with tetralogy of Fallot malformations do not experience life threatening symptoms in early infancy and for this large subgroup of patients, the choice of a palliative or corrective procedure is never a real consideration. For the larger child, usually larger than 12–15 kg, we recommend intracardiac repair even in the presence of complicating anatomical features such as anomalous coronary circulation.

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Discussion

DR. CLARENCE S. WELDON (St. Louis, Missouri): We looked at our data, and came up with a slightly different conclusion. We handled in our institution about 20 tetralogies a year, and this slide records data back to 1969. It's incomplete for the current year as it was done about six months ago. The operations are color coded, and arranged by year. Yellow is a total correction, and blue, green, and red are various kinds of shunts. Hospital mortality, where it occurred, is marked with an X, and an asterisk indicates an infant under one year of age done with deep hypothermia and circulatory arrest. The yearly mortality is indicated above each yearly group.

There is a clear evolution shown in the way we managed tetralogy. In this early period the corrective operation was reserved for children over five. Children under five had palliative shunts done. in the middle period we extended the reparative operation down to about age two, and reserved palliative shunts only for those children younger than two. In the recent period we have abandoned the use of palliative shunts, except for a few children who had pulmonary arterial atresia in conjunction with tetralogy anatomy.

It can be seen that despite the decreased use of shunts, there was an improvement in our overall mortality figures.

If you look at this mortality more closely, most of the shunt mortality was some time ago. There was one shunt failure, with persistent cyanosis and death. There were two infants who had operations which were thought to be unsatisfactory for the relief of cyanosis. They then had secondary shunt operations, and developed congestive heart failure and death. There was one tragic pneumonia in a child who had a shunt; and then there was an infant who developed necrosis of the bowel. So there was a 13% mortality in this series of shunts when we were doing them earlier.

Considering the mortality for total correction, there have been six of 87 (7.5%) children in this series who died following total correction. Two of them were early in the series. Both died of hemorrhagic atelectasis in the postoperative period. I think this is a preventable lesion. We don't see it anymore, and I think it was a consequence of excessive blood destruction, when we had a lot of suction during these operations, and when we primed the heart-lung machine with whole blood. We did have one uncontrolled intraoperative hemorrhage from an aorta which tore while we were taking down a Potts anastomosis. We had one patient who was a misdiagnosis. This child was thought to have shunt failure, but actually had an Eisenmenger reaction with far advanced pulmonary hypertension. We recognized this at the time of the operation, and unwisely went ahead with the correction anyway. We, of course, ended up with supersystemic pressure in the right ventricle and an intraoperative death. So that, really, is a misdiagnosis.

We have one patient where we couldn't relieve the obstruction because of peripheral pulmonary artery coarctations, and ended up with a very high pressure in the right ventricle, and postoperative low output failure.

And then we had a recent unexplained and unanticipated death in a child with Down's syndrome, who was extubated the next day, and suddenly died either from an arrhythmia or possibly from some form of respiratory arrest.

If we look at these deaths according to risk factor, we then have only one patient under two. There were eight patients under two, and that was the only death. No patients over twenty died. And the shunts didn't seem to be related, except for this one who had the Potts tear. There were eight children in whom we took down Waterston shunts and repaired the pulmonary artery. There were no deaths in that group.

So the way we came up with it was that an early correction is a good operation. It looked as though we were improving our results by doing early corrections. None of the five children who had repairs done under deep hypothermia and circulatory arrest, within the first year of life, died.

My thought this morning would be, therefore, that Dr. Bender and his colleagues deserve an enormous commendation, and perhaps the operation of repair in early life does not yet deserve a severe condemnation.

DR. JAMES B. DONAHOO (Baltimore): Our experience has been similar to theirs, and yet I would agree with Dr. Weldon on the fact that we would not completely condemn the early intraoperative correction in a child if the anatomy is favorable. While Dr. Bender's experience clearly indicates that, at least in Nashville, a preliminary shunt followed by correction is the operation of choice, I think other people's experience would indicate that there is at least some initial mortality in the small children that have undergone systemic pulmonary artery shunts; and coupled with the mortality of the operative correction itself, I think there is room for some primary intraoperative correction in these small children.

DR. HARVEY W. BENDER (Closing discussion): I don't mean to condemn the immediate primary correction in this data. Our bias was certainly that we had the feeling that the primary correction in these small infants was going very well, but I think we tended to include those patients with VSD's, transpositions, and other things; so that the results in the first year have been quite good. But when we looked carefully at our tetralogy data, there was a very distinct break at two years of age, with those patients having their operations over two all living, and a significantly high mortality in those patients under two. And yet, the overall mortality for the entire group was less than 5%.

In answer to Dr. Donahoo, I think you are absolutely correct. If there is a significant mortality with the shunt, and you couple this with the mortality of a subsequent procedure, it can creep up on you. I think the surgeon must keep shunt mortality very low, if you are going to do a two-stage procedure; but I believe that this can be done.

Circumflex Coronary Artery Bypass Grafting Via Transverse Sinus

ALLEN S. HUDSPETH, M.D.

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Grafting the circumflex coronary artery has been more difficult technically than the right or anterior descending because of its posterior location and the angles of its marginal branches. However, grafting this artery has been substantially simplified by a method wherein the graft is passed directly through the transverse sinus and anastomosed to the back of the ascending aorta. This follows the most direct course to the ascending aorta and the graft is much shorter than one brought anterior to the heart. There is little chance of kinking the graft, since its angle of attachment is ideal, and due to the anatomical configuration of the transverse sinus, there is more room for the graft and compression is unlikely. This allows more room on the anterior surface of the aorta for grafts to other coronary arteries. This method has been used in 50 cases and blood flows have been excellent. Twelve of these cases have been restudied postoperatively and the grafts are patent.

IN ORDER for coronary bypass surgery to attain the clinical objectives of stopping angina pectoris and preventing or postponing myocardial infarction and/or death, the technical objectives of reestablishing adequate blood flow to viable myocardium must be without flaw. The majority of descriptions and details of the technical aspects of aorto-coronary saphenous vein bypass grafting have been concerned mainly with the details of creating the anastomoses.[1-3] Certainly this is a critical consideration in this operation, however, I do not believe that enough emphasis has been placed on certain other technical aspects of managing these grafts. These include graft length, angles of attachment, avoidance of graft kinking, and course of the graft taken from the coronary artery to the ascending aorta. Problems of this nature are relatively minimal with vein bypass grafting of the right coronary and its branches and the anterior descending coronary and its branches. When grafting these two arteries, almost the only consideration necessary for the vein between the two anastomoses is that it be made long enough and, if so, it is easily placed in such a position as to avoid further problems. The graft to the right coronary usually assumes the course of the coronary artery, and if a relatively loose loop is placed in the anterior descending graft, it will assume, naturally, a good position over the pulmonary artery.

However, grafting the circumflex coronary artery has been more difficult technically because of its posterior location and the angles of its marginal branches. If this graft is brought anterior to the heart, its angle of attachment may not be ideal and there is much greater chance of kinking the graft or compressing it.

The purpose of this paper is to present a method which has simplified substantially grafting of the circumflex coronary artery.

Technique

The distal anastomosis is made using aortic cross-clamping and topical hypothermia. The graft is beveled and applied along the longitudinal axis of the recipient artery. If more than one of the marginal branches of the circumflex are to be grafted, the subsequent branch or branches are anastomosed side-to-side to the vein graft in sequence. The vein graft then is passed through the transverse sinus, which is the most direct route to the ascending aorta (Fig. 1). Care is taken at this point to

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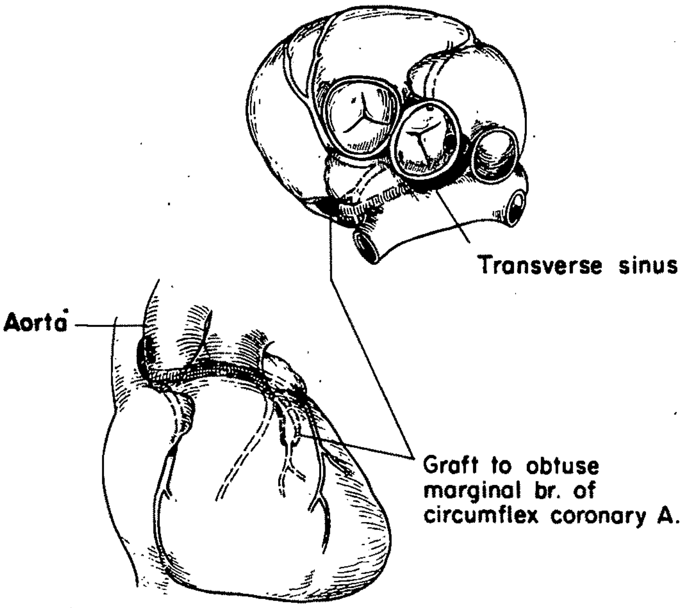

FIG. 1. Diagram showing vein bypass graft from obtuse marginal branch of circumflex coronary artery to ascending aorta via transverse sinus. Note anatomical relationship of transverse sinus and coronary arteries. Also, note direct route from circumflex coronary artery to ascending aorta and length of graft as compared to one looped anterior to the heart.

avoid twisting the graft. The aorta is unclamped and the heart is defibrillated. A bull-dog clamp is placed on the graft near the coronary artery, the vein is gently distended with blood, the heart is partially filled, and the length of the graft is carefully measured. The vein is cut squarely across at this point and the graft then is slit for 6–8 mm on its anterior surface. A partial occlusion clamp is applied to the back of the ascending aorta for the proximal anastomosis. This clamp usually is applied somewhat to the right of the true posterior and is applied just above the noncoronary sinus of Valsalva. Any problems with application of this clamp can be alleviated by reducing arterial inflow for a few seconds to allow aortic pressure to drop. I have used a relatively small partial occlusion clamp whose jaws are angulated slightly posteriorly. The aorta is then readily rotated with the clamp for excellent exposure for this anastomosis. The handles of the clamp are placed cephalad and the clamp usually can be attached to the left side of the drapes with a towel clip and does not require holding during the performance of the anastomosis. A 5–6 mm circular button of the aorta is removed with an adenoid punch, and the end-to-side anastomosis is made without difficulty. After the clamps are removed, both anastomoses and the entire length of the graft are inspected to insure hemostasis. Most of the time this graft cannot be seen readily when the patient is removed from cardiopulmonary bypass and the heart is full, therefore, I have routinely measured blood flow in this graft while the patient is still on cardiopulmonary bypass. Almost always when the circumflex coronary artery is grafted, other coronaries are grafted as well, and I have found it somewhat better to do the circumflex first.

Results and Comment

This method for grafting the circumflex coronary artery has been used in 50 patients. Forty-one of these patients have had only one distal anastomosis to the circumflex, while the other 9 have had two or more distal anastomoses done in sequence. When only one distal anastomosis was made, blood flows averaged slightly over 80 cc per minute, and with two or more distal anastomoses, blood flows averaged slightly more than 120 cc per minute. Twelve of these cases have been restudied postoperatively and the grafts are patent.

I have encountered virtually no disadvantages to this method. Certainly care must be taken not to twist the graft, since it might not be detected after the circulation is returned to the heart. Length of the graft must be reasonably accurate, however, there is a fair amount of room in the transverse sinus and the distended graft readily seeks a position to avoid kinking. An extremely long graft should be avoided, but the main consideration regarding length is that it not be too short. Any concern regarding the performance of the proximal anastomosis is not warranted. The clamp is easily applied and the aorta is readily rotated for excellent exposure for this anastomosis and, surprisingly, I find it easier to make than an anastomosis placed on the anterior surface of the aorta. Concerns regarding hidden bleeding from this graft after the patient is removed from bypass are real. However, this is true of the distal part of the graft and the distal anastomosis to the circumflex, no matter what method is used. The proximal anastomosis can be visualized without much difficulty by rotation of the ascending aorta, and the partial occlusion clamp can be reapplied if necessary. With reasonable care, all of these potential problems are avoided and I have not encountered this in dealing with this group of patients.

The use of this method has simplified grafting the circumflex coronary artery for me. The graft is much shorter than one brought anterior to the heart and with actual measurement, is less than one-half as long. There is almost no chance of kinking the graft, since its angle of attachment is ideal, and due to the anatomical configuration of the transverse sinus, there is more room for the graft and compression is unlikely. Two separate grafts are readily accommodated if required. As a matter of fact, on several occasions I have brought the vein graft from a proximal anterior descending diagonal sequence through the transverse sinus along with the circumflex graft and anastomosed it to the ascending aorta just above the circumflex graft. Using this course for the bypass graft to the proximal anterior descending and diagonal, has the same advantages as mentioned above. Obviously this allows more room on the anterior surface of the aorta for grafts to other coronary arteries.

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DISCUSSION

DR. IVAN K. CROSBY (Charlottesville, Virginia): We have collected some of the data of the last three and a half years at the University of Virginia, and have found that we were putting in about 2.8 grafts per patient; so a lot of patients get circumflex grafts.

I think we've used this technique about 30 times, and it's been technically very satisfactory from our point of view. We haven't had any complications in terms of bleeding or early occlusion.

However, it think that it's not the perfect answer for the circumflex. I think the left atrial appendage sometimes gets in the way when you are putting a graft to the main circumflex artery distally in the atrioventricular groove; and I think in that situation the conventional anterior graft is more appropriate.

I think we can take a little more precaution in demarcating this anastomosis for our cardiologists, and we won't leave them wondering where that single silver clip is. We put a metal ring around that anastomosis, because I think they may have some difficulty finding that graft to restudy it.

I think that brings up the question of whether as many of these grafts stay open at one and two years as those placed in the conventional anterior position.

DR. ALLEN S. HUDSPETH (Closing discussion): I can't answer Dr. Crosby's question. Obviously, it's going to take a long time to answer many questions in coronary artery surgery. It obviously is going to prove to be a tremendous statistical surgical maneuver, and my point of view about it is that coronary artery surgery is not fun; the results of it are fun.

I have been working on this stuff commonly, day to day, and make many comments in the operating room. One of my favorite ones is that if Job had had to do this, he wouldn't have gotten very much publicity. So I don't know.

I think it is so critical technically. I think that this type of surgery probably is the most demanding technically that I have done. You can work for hours on these patients, and make one 1 mm error, and ruin the whole thing. That's what we're dealing with.

So I have thought that any technical consideration that seems beneficial in anyone's experience probably should be shared with others, and that was the reason for presenting this.

False Aneurysms of the Femoral Artery:

A Challenge in Management

CARLOS M. CHAVEZ, M.D., F.A.C.S.

Forty patients with aneurysms of the femoral arteries were evaluated. Thirty had 34 false aneurysms and 23 were secondary to disruption of the suture line of a graft-to-artery anastomosis. All the false aneurysms were found in association with a synthetic material used as a bypass or arterial substitute. No direct relationship was found between the suture material and the incidence of anastomotic aneurysms in this series. Infection associated with the development of a false aneurysm was followed by a high incidence of amputation. Various techniques of repair have been used to restore the flow and preserve the viability of the limb. Recommendations are made to decrease the incidence of this complication.

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WITH THE WIDESPREAD USE of synthetic arterial substitutes complications inherent to these materials have been reported with increasing frequency. These are related to the fabric prosthesis itself or the suture material used for the anastomoses.[1,4,7,10] Among the most significant complications associated with the use of artificial prostheses are infection and the development of false aneurysms.[5] In many cases these two complications are directly related but each may be a serious problem in management.

A review of our vascular surgical experience for the past 10 years at the University and Veterans Administration Hospitals in Jackson, revealed a total of 40 patients with aneurysms of the femoral arteries. An analysis of these cases and the lessons we have learned will be discussed here.

Material and Analysis

Forty patients with aneurysms of the femoral artery were treated at the University or Veterans Administration Hospitals. Thirty patients had false aneurysms and ten had true arteriosclerotic aneurysms. Our study will be limited to those patients who developed false aneurysms. The average age of these patients was 59.7 years. There were 27 males and 3 females.

Thirty-four false aneurysms were found in 30 patients. It is interesting to note that two patients developed recurrent false aneurysms, each one having a total of three. In addition two patients also had associated true aneurysms in other areas. Of the entire group of false aneurysms, 10 were secondary to various types of trauma: the nature of this could not be determined in one of our patients. The remaining group of 19 patients developed false aneurysms as a result of disruption of the anastomotic suture line of a graft to the host artery (Table 1). One patient of this series developed an aneurysm in the distal superficial femoral artery near the distal end of an onlay vein graft performed three years earlier. It was not possible to determine its nature, although it is likely that it was of a true type since two years following its repair the patient developed a true aneurysm of the common femoral artery on the same side. If we consider this to be the case, none of our patients has had a false aneurysm in an autologous vein graft. In fact, all false aneurysms in our series developed in those cases where synthetic material (Dacron) was used as an arterial substitute.

Of the 23 false aneurysms secondary to disruption of the graft anastomosis, 22 occurred at either the common femoral artery or its bifurcation; 14 of these were in pa-

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TABLE 1. *False Aneurysms of the Femoral Artery (30 Patients)*

Suture line disruption	23
Trauma	10
True vs false	1
Total aneurysms	34

tients who had had aorto-femoral or axillo-femoral grafts. In one instance a false aneurysm developed at the suture line of a Dacron femoral graft replacement. Eight false aneurysms were found following femoro-popliteal bypass procedures and in 7 the false aneurysm occurred at the site of the proximal anastomosis (Table 2).

The length of time between the operative procedure and the appearance of the false aneurysm varied from two months to 13 years with an average interval of 47.5 months.

There were 4 deaths in this series, but none of them was related to the surgical procedure itself. Four patients underwent major amputations as a result of infection and/or thrombosis of the femoral vessels following repair of the false aneurysm.

Suture Material. In reviewing the operative reports of all patients with false aneurysms following prosthetic bypass procedures, it was possible to obtain information about the suture material used for the anastomoses in 13 cases. In five, the graft was anastomosed using silk sutures and in eight the prosthesis was anastomosed using synthetic suture material (Mersilene or Prolene).

Contrary to previous beliefs the use of synthetic fibers for vascular anastomoses has not drastically influenced the development of false aneurysms in our experience. I believe we will continue to see these complications despite the widespread use of synthetic suture material and almost total abandonment of silk for this purpose.

Presence of Infection. In only one instance, infection was associated with the development of a false aneurysm. In the overwhelming majority of cases, no evidence of infection was found either preoperatively or at the time of surgery. However, infection developed following repair of the false aneurysm in 5 patients and in 4 this was followed by amputation of the corresponding extremity. The fifth patient died as a result of a ruptured abdominal aneurysm shortly after the repair of the false aneurysm. The presence of infection was determined at the time of the postmortem examination.

TABLE 2. *False Aneurysms Secondary to Graft-artery Disruption*

Location		
Aorto-femoral graft	13	14
Axillo-femoral graft	1	
Femoro-popliteal bypass		
Proximal suture line	7	8
Distal suture line	1	
Femoral graft interposition	1	
Total		23

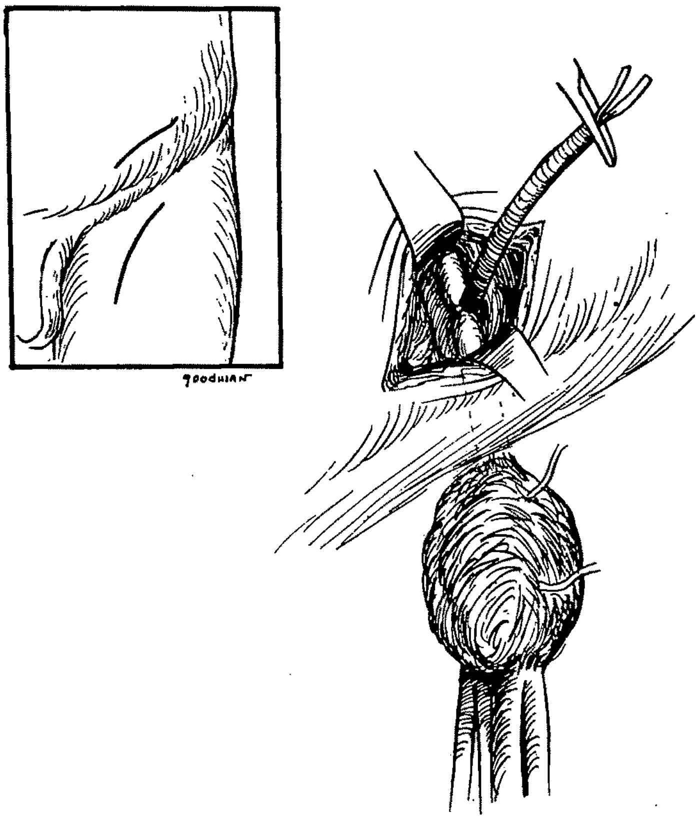


FIG. 1. Extraperitoneal approach of the iliac vessels can be easily performed using a separate incision above the inguinal ligament (Insert). The false aneurysm is then exposed for repair below.

Surgical Technique. Planning of the operative procedure with due consideration to all the alternatives in the event of unusual findings is of utmost importance. Most of these operations have been performed under spinal or general anesthesia depending upon the condition of the patient. The abdomen, groin, and legs are thoroughly scrubbed and draped..

Control of Arterial Inflow. Operative exposure and control of the arterial inflow to the false aneurysm should be the initial step prior to the dissection of the aneurysmal sac. The proximal portion of the common femoral artery can be reached through the same incision made to expose the false aneurysm; however, if more proximal control is necessary this can be better made using an extraperitoneal route. The extraperitoneal approach has been found very useful for the control of the external iliac artery and the proximal control of the corresponding limb of the graft in the case of an aorto-femoral bypass (Fig. 1).

Handling of the Aneurysm and Repair. Dissection of the entire false aneurysm is not necessary and often is dangerous. Identification of the vessel distal to the

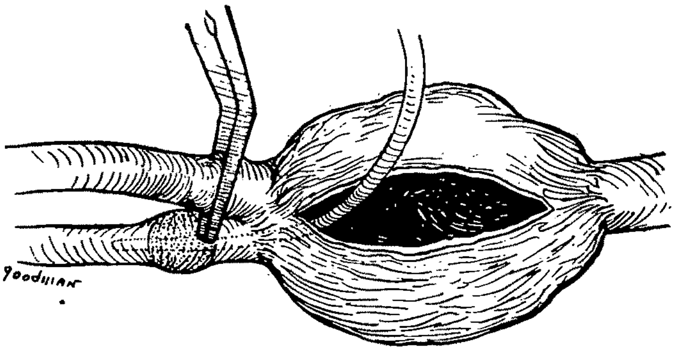


FIG. 2. Bleeding from the arterial branches connected to the aneurysmal sac can be controlled by insertion of a balloon catheter inside the vessel inflating the balloon until the bleeding stops.

aneurysm is rather difficult and should not be attempted. In most instances an extensive fibrous reaction surrounds the false aneurysm, the prosthesis and arteries involved. It is easy, under these circumstances to injure the profunda femoris or one of its major branches with resulting profuse bleeding. Attempts to control the hemorrhage may lead to obliteration of an important arterial branch. Furthermore, time spent in unnecessary dissection along with the repair of any possible injury to other vessels encountered as a result of the dissections will prolong the operating time with increase in the incidence of wound contamination, and potential graft infection.

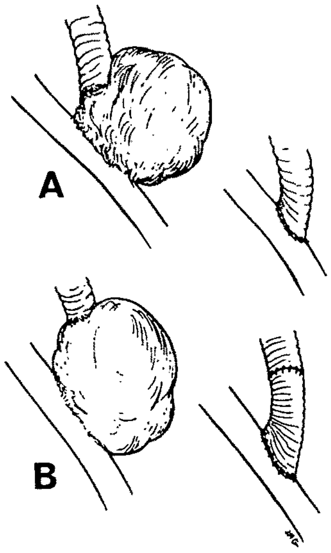
The patient is systemically heparinized and the arterial inflow occluded. The aneurysmal sac is entered and the necrotic material and clotted blood are removed. At this moment bleeding may be noted from the distal vessels when the collateral circulation is sufficient. The retrograde bleeding from the distal vessels attached to the false ansurysm is controlled by either hand pressure or the insertion of a balloon catheter inside the vessel, inflating the balloon until the bleeding stops (Fig. 2). Once a dry field is obtained the proximal and distal vascular lumens are identified and the correction of the situation can be carried out in the most effective manner.

Type of Repair. In most instances the same graft material was used for repair of the defect created by the false aneurysm. Re-approximation of the graft is sometimes possible, especially when part of the suture line remains in place (Fig. 3a). This was feasible in 6 cases of our series. Re-anastomosis of the graft to the host artery can then be performed in the usual manner but this time a re-enforcement of the arterial wall with Teflon felt is considered of importance to prevent disruption of the arterial wall with the sutures.

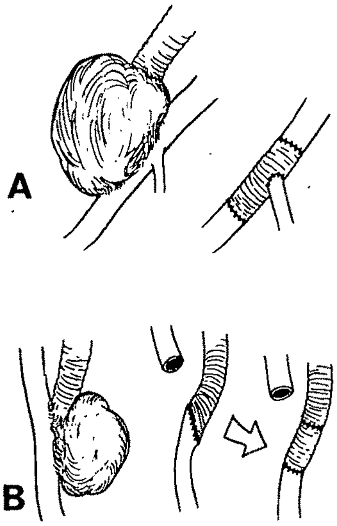
In those cases where total separation of the graft has developed a segment of a prosthetic (graft) can be interposed between the previous graft and the host artery (Fig. 3b). This type of repair was performed in the majority of patients in our series. Here again, the anastomosis to the artery should be reinforced with Teflon felt. Undue tension on the suture line is also prevented by the addition of length to the existing prosthesis. The anastomosis is facilitated by preservation of the fibrotic tissue by partially opening the aneurysmal sac and avoiding extension of the incision through and beyond the previous anastomotic site.

Removal of the graft, particularly when thrombosis of the latter had developed in conjunction with a false aneurysm, was carried out in four patients with false aneurysms of the proximal anastomosis of a femoropopliteal bypass. In three of these cases an attempt was made to revascularize the profunda femoris by a patch graft of autologous vein or prosthetic material. In all three patients this procedure failed to prevent progression of the ischemic changes already present and amputation was inevitable. In the remaining patients a variety of procedures was used according to the situation encountered (Figs. 4a and b and 5a and b).

Repair of a post-traumatic false aneurysm is frequently an easy surgical task.[2] When the defect in the artery is small it can be repaired with simple sutures of nonabsorbable material, after evacuation of the hematoma from the false aneurysm. If the extent of the defect is such that a direct closure is not possible, this segment is excised and a direct end-to-end anastomosis of the divided artery is performed. This is not always possible because of the excessive amount of damaged artery excised; if there is any question in regard to excessive tension prior to or following the anastomosis, interposition of a graft is indicated. This should preferably be an autologous tissue such as the saphenous vein; but if this vessel is inadequate in size or the saphenous vein has been removed, prosthetic material can be used provided no infection is present at the time of the repair.



FIGS. 3a and b. a) Re-approximation of the initial graft to the host artery is sometimes possible after careful resection of the false aneurysmal sac. b) Retraction of the graft and total detachment, as shown in the figure, will require interposition of a new segment of prosthetic material to bridge the distance and decrease tension on the suture line.



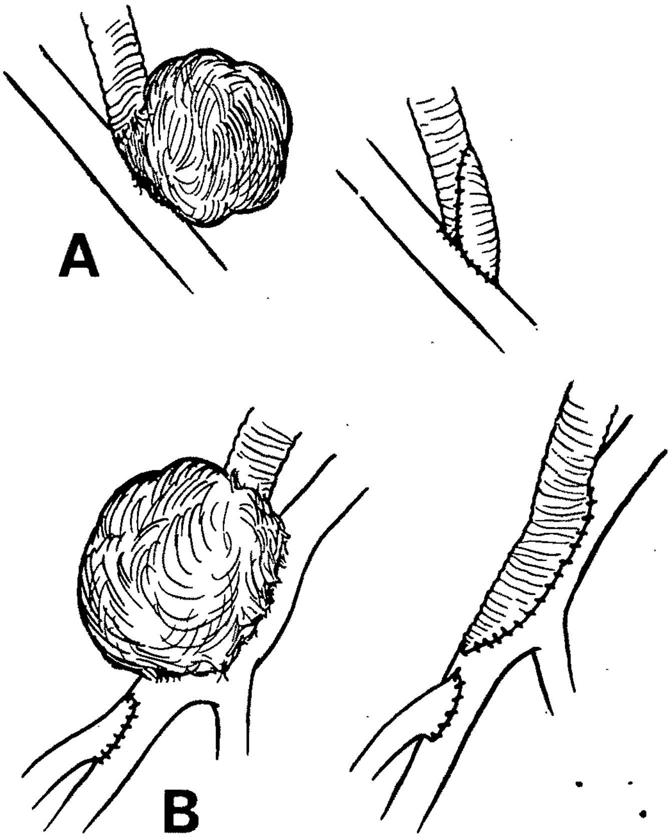
FIGS. 4a and b. a) Trimming of the graft or host artery during resection of the aneurysmal sac can make necessary the use of a patch graft to maintain an adequate anastomotic lumen. b) Resection of the anterior part of the aneurysmal sac may help in preserving the take-off of the profunda femoris. A patch graft constructed with the distal segment of the dacron graft will cover the defect.

All necrotic tissue and hematoma should be removed and intra- and postoperative administration of antibiotics should be initiated.

Discussion

The presence of a false aneurysm secondary to disruption of an arterial anastomotic suture line should be considered as a surgical emergency. Even though false aneurysms secondary to trauma should be treated surgically as soon as possible, their treatment is not as urgent as that of the anastomotic aneurysm. The most common locations for the occurrence of the anastomotic aneurysm are the abdominal aorta and the femoral region.[9,11,12] This is proportional to the number of arterial procedures performed in these locations. However, it is interesting to note the low incidence of anastomotic aneurysms in the distal anastomosis of femoro-popliteal bypasses. From the factors mentioned as responsible for the occurrence of anastomotic false aneurysms the suture material used has not proven to be of such capital importance as once was thought; the reports of Moore[7] and Gardner[6] emphasized the important role of silk sutures in the development of these aneurysms. Recent experience, however, has denied the substantial role assigned to this factor. In our series false aneurysms occurred no more frequently when arterial anastomosis was performed with silk than with other synthetic suture material. There is substantial evidence that infection plays a significant role in the development of false aneurysms which occur early in the postoperative period following the insertion of an arterial graft.[10] However, these aneurysms are rather infrequent; the majority of patients develop false aneurysms several months following the initial procedure. The average time elapsed from the vascular procedure to the diagnosis of a false aneurysm was 31.8 months in the series of Nunn and associates[8] and 5 years in that of Gardner and associates.[6] In Gardner's series only 3 of a total of 37 false aneurysms were secondary to, or associated with infection and they occurred at a mean time of two months after the initial vascular procedure. In our series the average interval between the initial procedure and the development of a false aneurysm was four years; infection was associated with the development of false aneurysm in only one case of a total of 23 false aneurysms.

There is substantial evidence that anastomotic false aneurysms develop almost exclusively when a synthetic prosthesis has been anastomosed to the host artery. Of these cases the overwhelming majority have developed by, or secondary to, the disruption of the suture line with the graft found partially or totally detached from the artery to which it was anastomosed. It has been observed that in most of these cases the sutures are attached to the graft that has pulled away from the artery. In only exceptional cases an aneurysm has developed due to the defect in the wall of the prosthetic material.



FIGS 5a and b. a) An alternate method for the preservation of the profunda femoris is reimplantation of this vessel in the graft used to replace the segment of the femoral artery resected with the false aneurysm. b) In one patient of our series with a false aneurysm at the distal anastomosis of a femoro-popliteal bypass, an end-to-end anastomosis was performed which ultimately required a graft interposition for recurrent stenosis.

The isolated cases reported where a "false" aneurysm was found in association with the use of an autologous graft have provided only questionable evidence that the false aneurysm developed as a result of the disruption of the suture line. In most instances there is evidence that the aneurysm developed at the wall of the vein rather than at the anastomosis. This may be the result of either a pathological vein wall or the excessive stripping of the adventitia from the vein. We maintain, therefore, that the tissue ingrowth between an autologous vein and the host artery is a significant factor in the exceptional occurrence of a false aneurysm in those patients who received a vein graft.

What, then, is the common denominator in the development of false aneurysms?

Reviewing our experience and that of others, no single factor can be isolated as decisive in the occurrence of this complication. Several contributing elements were found, however, in many of these patients; these factors include trauma to or near the area of anastomosis, associated systemic arterial hypertension, and in a few cases, the presence of infection. The condition of the arterial wall should be considered as a possible contributing factor, since it is not unusual to find more than one false aneurysm in the same patient.[3] Secure placement of the sutures during the anastomosis is particularly important, although it is not always possible without sacrificing the adequacy of the anastomotic lumen. In cases where the arterial wall is rather thin or friable re-enforcement of the sutures should be carried out with backing material of pledgets strips of Teflon felt, or autologous vein wall.

Autologous vein and Dacron substitutes are at the present time the most readily available and satisfactory grafting materials. Dacron prostheses have proven effective and are unsurpassed for bypass or substitution for large and medium size arteries (aorta, iliac and proximal femoral). Saphenous vein grafts, on the other hand, are far superior to any fabric prosthesis for patch grafts or arterial substitutes below the inguinal ligament and bypass for small arteries (renal, coronaries, and carotid.)

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DISCUSSION

DR. ALTON OCHSNER, JR. (New Orleans): I think this paper by Dr. Chavez is important, and one of the most important things that he has told us is that this false aneurysm can occur with other than silk suture materials. For years we thought it was the silk we used on the earlier anastomoses.

I do think it's important, however, that we differentiate early false aneurysms from acute bleeding from late anastomotic aneurysms, and arteriosclerotic aneurysms, because, although from a technical standpoint they are similar problems, I'm not sure that we can equate those from a prognostic standpoint.

I have never seen a late anastomotic aneurysm cause trouble, other than slight discomfort. They are operated on because they are there, and as Dr. Chavez has shown, not without some risk sometimes to the extremity. But I do subscribe to the early operation theory, because the smaller the aneurysm, obviously, the easier the operation, the less technical difficulty you are going to have.

However, in one patient I elected to follow the femoral aneurysms that he had (late anastomotic type) because he had extensive arteriosclerosis (coronary, cerebral) and had such poor anatomic runoff in the extremities, I felt if I were to operate upon him, if I did not kill him, I certainly took a good chance of causing a loss of limb. I followed him for almost a 15-year period, until he died of a myocardial infarction. In this time he had absolutely no trouble from these aneurysms, although I did watch them grow from a small orange to a medium grapefruit size.

The point is, we know these aneurysms grow. What we really don't know is the true incidence of complications from these late anastomotic aneurysms; that is, the chance of hemorrhage, thrombosis, and distal embolism.

I was interested to see that Dr. Chavez presented some late anastomotic aneurysm problems of the femoral-popliteal bypass, because I always wondered why I had never seen a late anastomotic aneurysm in a femoral-popliteal bypass. I presume that they don't present as clinical aneurysm problems. They probably present as thrombotic grafts, and are not recognized, perhaps, as aneurysms.

Now, the technical problems of correcting anastomotic aneurysms are great, as Dr. Chavez has pointed out. It should make us consider bypassing to the external iliac artery more frequently, especially when the femoral vessels are relatively normal and the pelvis is shallow. Anastomotic aneurysms, if they were to occur at the site of a graft of the external iliac artery, are most easily handled by dividing the graft and ligating the iliac artery proximally and distally, and then extending the bypass to the virgin femoral artery.

President Muller: It seems that we have a bit of sibling rivalry here, because the next discusser is Dr. John Ochsner, of New Orleans.

Dr. John L. Ochsner (New Orleans): Dr. Chavez suggests in his paper that the suture material really is of secondary importance in anastomotic aneurysms.

(Slide) The healing of a vascular anastomosis is very similar to the healing of any wound. In the early lag phase of healing it takes very little to pull it apart, because there is no elastic tissue growing across the anastomosis. By the forty-fifth day of healing, however, the anastomosis—and this is of autogenous tissue—is actually as strong, if not stronger, than the adjacent host tissue, or the adjacent vessel, as measured by the tension on the anastomosis, as well as the bursting force within the intraluminary cavity.

(Slide) As you can see, in that situation of an anastomosis between autogenous tissue, it really doesn't matter what the suture material is, as long as it lasts 45 days.

Now, in contrast, the anastomosis between a prosthesis and a host vessel relies upon the continued presence of the suture itself, because there is nothing but fibrous tissue as a bond between the prosthesis and the host tissue.

(Slide) There are many factors, and Dr. Chavez aludes to this in his manuscript, that cause, or play a part, in the production of an anastomotic aneurysm. Although he thinks it's of secondary importance, it does have a primary role, and that is the suture material itself. It has to be a nonwettable substance. It should be strong. It shouldn't fragment, and it should retain its strength and be at least as strong as the plastic, or whatever the prosthetic material is.

The type of graft is important, in the sense that if it's a woven graft, one must avoid the chance of fraying, and take deeper bites. If it's a knitted graft, one need not worry. It should, again, be made of nonwettable substance, and should not fragment, such as we found happened with the old nylon grafts.

The next is the relationship to a joint. It shouldn't cross a joint, or the anastomosis shouldn't be made where the movement is maximal, because, if one does, there is always the axial stress by the motion of the joint placed on the suture line itself.

The type of anastomosis—it's obvious that one has to have a bloodtight anastomosis, so that hemorrhage doesn't occur, or hematoma around the graft.

Of more importance in the femoral area, one must be sure that the external elastic membrane is incorporated into the suture. This is the strength of that particular vessel, and you can have all the adventitia and the intima and media, and have nothing, if you don't have the external elastic membrane.

The compliance of the graft is also important. We have never been able to manufacture the ideal graft, where the graft can have the same distensibility as the host vessel. All these grafts eventually become fixed with the fibrous tissue, so there is a shearing effect, or shearing stress, between the graft and the host vessel, because of the continued distensibility of the host vessel, and yet none of the graft.

Now, this can be minimized if one makes sure that the graft, or the diameter of the graft, is 1.4 times that of the host vessel; but be that as it may, there will still be a shearing stress on the anastomosis. Despite this, the force will be less than one tenth of that of the suture material that one employs. Any of the synthetic materials used today are at least ten times the strength of the shear stress put on anastomosis.

So what happens, as Dr. Chavez has shown, is, it pulls away, or through, the vessel; so the important thing is, really, then, the state of the host vessel. If the host vessel is a good vessel, and if it has an intact external elastic membrane, and one sutures this, the chances of production of a false aneurysm are very small.

And, of course, the last, but still important, is that infection will always produce a false aneurysm in the presence of prosthesis.

Dr. William H. Edwards (Nashville): Our experience parallels Dr. Chavez's, in that the false aneurysms which we have encountered have been primarily at the femoral anastomosis of an aortofemoral bypass graft. I would add one word of caution; that the surgeon who is dealing with a false aneurysm at the femoral level needs to be absolutely certain that the aortic anastomosis does not carry a similar aneurysm.

I feel that the etiology of these aneurysms is probably a combination of factors, if you rule out the infection, which, of course, is an etiologic factor in the acute aneurysm. These factors are the disease process which is present in the host vessel, the hypertension which many of these patients have, and the tension which is obviously placed on this prosthetic graft as it crosses the inguinal ligament, or beneath the inguinal ligament, must be a factor.

We attempt to place the anastomosis as high on the common femoral artery as is technically possible.

I would like to make one final comment on my technical approach in the aneurysm, which differs a little from Dr. Chavez's. I do prefer to dissect out the runoff vessels, or the distal vessels, prior to opening the aneurysm. I feel that the runoff vessels are extremely important to maintain viability of the extremity. I like to have these vessels dissected out prior to opening the aneurysmal sac.

I also feel that proximal control can be obtained through the inguinal ligament. Exposure of the Dacron prosthesis is very easy if one gets right down onto the fibers of the Dacron bypass, and proximal control can then be obtained.

I also feel that, once this aneurysm has occurred, the interposition of another short segment of Dacron is probably superior to trying to patch or reconstruct the anastomosis, which, for obvious reasons, has already undergone trauma, and has pulled apart.

Dr. Daniel B. Nunn (Jacksonville, Florida): Two years ago we reported 12 anastomotic false aneurysms all of which followed Dacron grafting using braided Dacron sutures. Five of these false aneurysms were caused by infection and the remaining seven aneurysms located in the femoral area after aorto-femoral grafting were thought to have been caused by placement of the grafts under excessive tension. In each instance these sutures were intact in the graft but had pulled out of the host artery.

(Slide) I also would like to comment on some of the factors affecting the occurrence of anastomotic aneurysms. Dr. Ochsner has already referred to the fact that woven grafts fray. Because of this, such grafts should not be used for end-to-side anastomoses. I wish to emphasize that careful operative handling of all grafts is essential since mechanical stretching and improper use of instruments may distort or disrupt synthetic graft fibers.

With respect to suture material, we personally prefer braided Dacron sutures rather than monofilament polypropylene sutures since surgical knots made with braided Dacron are significantly more secure.

The condition of the host artery has already been mentioned. We wish to emphasize that the degenerative arteriosclerotic changes that occur in the host vessels weaken the vessel from the standpoint of its ability to hold sutures. In this regard, we feel that care should be taken to insure that sutures incorporate large bites of the host vessel. When there is excessive friability it may be advisable to use horizontal mattress sutures with dacron or teflon pledgets.

It is also important to point out that aneurysmal dilatation of the host artery can be prevented by wrapping the artery with a cuff of dacron material.

With respect to the type and location of anastomosis, it has already been mentioned that the femoral area is the most common site of anastomotic false aneurysms. This particular area is one of the less clean areas of the body, and an anastomosis in this location is protected only by the skin and subcutaneous tissues unless a flap of sartorius muscle is used to cover the anastomotic site.

It should also be noted that an end-to-side anastomosis produces turbulence and decreased flow rate at the anastomotic bend because of the disturbance in pressure brought about by the abrupt change in direction of flow. The energy resulting from this turbulence and change in flow rate is distributed in part to the anastomotic suture line and can be a significant factor contributing to the development of a false aneurysm.

Excessive traction on a graft in the femoral area is an important etiologic factor which can be produced by both hip motion as well as placement of the graft under too much tension.

Hypertension and postoperative anticoagulant therapy promote the development of false aneurysms primarily by potentiating leaks at the anastomotic suture line. Consequently, an aneurysm may occur either as a direct result of the leak, or may follow secondary infection of a hematoma. In addition, the increased pulse pressure related to arterial hypertension may be an etiologic factor.

In an effort to decrease the incidence of anastomotic aneurysms we have used the technique described by Barker in which a cuff of Dacron is placed around the aortic graft suture line. Although the use of this technique has probably decreased the incidence of anastomotic aneurysms, we have observed aneurysms in two patients in which the cuff slipped out of position. Possibly this could be avoided by suturing the cuff to the proximal aorta as well as the graft.

(Slide) Another technique that we have been interested in is the use of an end-to-side Dacron cuff to cover the femoral anastomosis. The cuff is constructed by performing an end-to-side anastomosis with two 3 cm segments of Dacron graft measuring slightly larger in diameter than the bypass graft and host artery. The segment of dacron designed to cover the host artery is split longitudinally, as you see in the illustration, and the entire supporting cuff is slipped over the end of the bypass graft before the end-to-side graft anastomosis is performed.

In order to minimize the risk of infection we continue to use prophylactic antibiotic therapy and avoid whenever possible concomitant procedures which would result in bacterial contamination. We also believe that anticoagulant therapy should not be administered following grafting.

Dr. Jere W. Lord, Jr. (New York, New York): Our experience is similar to reports in the literature and Dr. Chavez's fine paper today including the discussers. Most of these aneurysms have occurred in the femoral region, in aorto-femoral bypasses and femoro-popliteal bypasses with synthetic prostheses. We have, therefore advised all of our patients as a result of two or three unfortunate experiences to avoid heavy sports. One tennis player, developed an aneurysm one year postoperatively following a strenuous game. Hence, motion of the hip joint, as was mentioned by one of the previous speakers, should be allowed only in normal activity.

Secondly, during the past year we have been dividing the inguinal ligament in all bypasses not only from the aorta to the femoral, but also from the common femoral artery to the popliteal. In some patients there is a narrow, tight canal. By cutting the inguinal ligament, more room is noted and perhaps there will be lessened shearing force on the prosthesis. With stenosis eliminated there should be no poststenotic dilatation. So far there have been no postoperative hernias.

In addition to Dr. John Ochsner's and Dr. Nunn's seven indications of why these people develop false aneurysms, there may be an eighth. Possibly the patient himself is the source of the trouble without an explanation. Obviously, that may be a matter of ignorance, and in time the explanation will become evident. I'd like to cite briefly the experience with a 48-year-old man examined in 1967 for severe intermittent claudication. (Slide) The preoperative aortogram showed an area of stenosis in each common iliac artery. We carried out an aorto-bilateral external iliac artery bypass. In 1967 we thought it wiser not to go to the femoral arteries. Later, Dr. Blaisdell and others have suggested that it is better to go to the femoral arteries.

In any case he did well for six years but reappeared in 1973 because of a return of claudication. He had lost 50 pounds of weight without explanation. His examination was negative except for weak peripheral pulses. An aortogram showed an interesting phenomenon. There was a large false aneurysm of the prosthetic-aortic anastomosis and false aneurysms at the anastomosis of the prosthesis to each external iliac artery. Also of interest was that the aorta still was patent, as well as the bypass. He was operated upon in the fall of 1973. The prosthesis was removed, the three aneurysms were inactivated and a new prosthesis was placed between the aorta and both common femoral arteries. Again he did well until the spring of 1975, when a false aneurysm appeared on the right side which was corrected by interposition of a prosthesis between the external iliac artery and the superficial femoral artery. Again this autumn, six weeks ago, a new false aneurysm appeared on the left side, and was operated upon in similar fashion. We have no explanation for problems this patient presents. There was no infection. Originally silk was used for the anastomoses but in the second, third and fourth operations Dacron sutures were employed. There may be a rare patient who defies all the known causes for aneurysmal formation in this region in spite of everything one can do. Or possibly the future will have an answer for this case.

Dr. Herbert B. Wren (Texarkana, Ark-Tex): A recent patient prompts a question I have for Dr. Chavez. A 60-year-old man had an iliofemoral prosthesis done two years ago for occlusive disease. He presented with a pulsating mass in the inguinal area. This was thought to represent an aneurysm due to anastomotic disruption. However, when he was operated upon, and the aneurysm was exposed, it was seen that, instead of arising at the distal anastomosis, the aneurysm in fact arose 2 cm proximal to the anastomosis, in a 2 cm slit in the graft itself. The aneurysm was trimmed away, and the graft was closed.

The question is: Although Dr. Chavez doesn't describe any patients like this, has he seen any patients where the aneurysm actually arises from the graft, rather than from the anastomosis?

Dr. Carlos M. Chavez (Closing discussion): In answering Dr. Alton Ochsner, I'd like to say that acute aneurysms are usually secondary to infection. Whenever we see an aneurysm develop within the next three or six months following an aorto-femoral or any other bypass procedure, we immediately think of infection as the cause of the aneurysm. We can, of course, have the development of false aneurysms in patients in which heparin has been given during and after the operation.

In any case, most of our cases have been delayed aneurysms, so we can not really say that most of these patients have been secondary to infection; and therefore, we have to implicate other factors in this.

We believe strongly that repair should be done as soon as the aneurysm is diagnosed, and the reason is because of the unfortunate experience that we and others have had in the past in treating some of these cases. Two of our patients developed thrombosis of the false aneurysm in the femoral artery, and another one came in with a rupture of the aneurysm into the pelvis and groin, which required emergency treatment.

Dr. John Ochsner has explained some of the factors that may account for the development of these false aneurysms, but I would like to point out that we have not seen a false aneurysm in an autologous vein graft anastomosis. I think that the statements he made in regard to the healing of any vascular anastomosis are valid for autologous vein grafts. Maybe this is one of the reasons why we don't see these aneurysms in the suture line of vein grafts. We have seen true aneurysms of the vein itself, and also we have seen true aneurysms in patients with false aneurysms, but these are two different things.

Dr. Edwards has pointed out that he prefers dissection of the distal branches of the aneurysm and of the false aneurysm itself. We tried this on a few occasions. However, the tremendous inflammatory reaction around the false aneurysm makes this very difficult and sometimes dangerous, injurying some of the branches. Therefore, we prefer to obtain only proximal control, open the aneurysm, look inside, and do the necessary repair.

We are aware of Dr. Nunn's excellent paper on false aneurysms.

We haven't divided the inguinal ligament as a routine.

Dr. Wren, we have seen also, as I said before, true aneurysms associated with prosthetic grafts, but not at the suture line. I am aware of previous cases reported in the literature of false aneurysms developing in the wall of a prosthesis. We have not seen one case where the false aneurysm developed at the prosthetic material. I think these aneurysms have been explained in the cases reported as secondary to defects in the manufacture of the fabric prosthesis.

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Peripheral Arterial Injuries:

A Reassessment

HUGH F. BURNETT, M.D., CLIFTON L. PARNELL, M.D., G. DOYNE WILLIAMS, M.D., GILBERT S. CAMPBELL, M.D.

Ninety-four patients with peripheral arterial injuries were subjected to acute repair, negative exploration, or late repair of the complications of the arterial injury (false aneurysm, A-V fistula, and/or limb ischemia). The causes of failure after acute injury include extensive local soft tissue and bony damage, severe concomitant head, chest or abdominal wounding, stubborn reliance on negative arteriograms in patients with probable arterial injury, failure to repair simultaneous venous injuries, or harvesting of a vein graft from a severely damaged extremity. There is a positive correlation between non-operative expectant treatment and the incidence of late vascular complications requiring late arterial repair. Delayed complications of arterial injuries occurred most frequently in wounds below the elbow and knee.

DIRECT REPAIR of human arterial injury with end-to-end union of a femoral artery was performed by Murphy in 1897.[7] Limb salvage after major arterial injury posed a problem through World War II. DeBakey and Simeone reported an amputation rate of 40% in 2,471 battle injuries involving arteries.[8] Direct arterial repair was initiated and extensively used during the Korean conflict, and the amputation rate dropped to 13%.[15] The failure rate of arterial injury repair has remained virtually static since the Korean experience.[9,12,17,24,26,33,38] As in any area of endeavor, periodic reassessment of results may identify the factors which prevent improvement. Accordingly, we have undertaken this review of our recent experience with arterial injury in order to delineate these factors. We have felt that a critical analysis of patients with failed repairs would be particularly enlightening.

There have been several excellent reviews of the diagnosis and management of acute arterial injuries.[9,12,17,20,24,30,36] However, late complications of missed arterial injuries (false aneurysm and arteriovenous fistula) indicate that the acute management of arterial injuries is not yet optimal.

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Little Rock, Arkansas 72201

Clinical Material

All patients undergoing surgery for suspected or proven arterial injuries or their complications between 1972–1975 were reviewed. The patients were seen by the General Surgery Service at the University of Arkansas for Medical Sciences either acutely or in consultation with the Orthopedic Surgery Service. The group was comprised of 94 patients who were divided into one of the following three categories: 1) Those undergoing acute repair, 2) those undergoing negative exploration, 3) those undergoing late reconstruction for the complications of a missed arterial injury. Patients were analyzed with regard to mechanism of injury, site of injury, extent of soft tissue damage, presence of associated fractures, presence of associated major venous injury and its repair and the harvest site of autogenous vein graft. Patients undergoing negative explorations were analyzed relative to the site of injury and complications directly related to the exploration. Patients with complications of missed arterial injury were reviewed with regard to method of initial management and length of delay before definitive repair.

There were 70 males (75%) and 24 females (25%) in the

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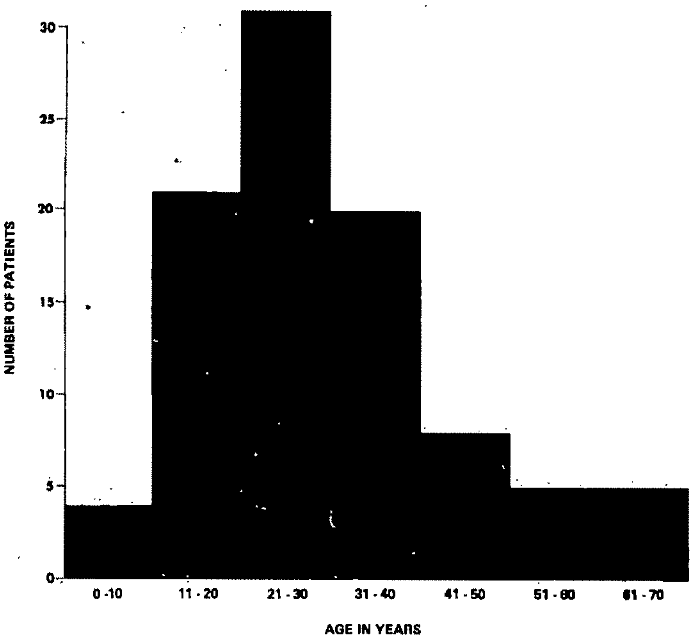

FIG. 1. Age distribution of patients.

group. The mean age was 30 years with a range of 4–68 years. The age distribution is seen in Fig. 1.

Acute reconstruction accounted for 49% of the operations performed, followed in order by negative exploration and later arterial reconstruction (Table 1).

Mechanisms and Sites of Arterial Injuries

The mechanism of injury in the 94 patients reviewed is seen in Table 2. Penetrating gunshot wounds were divided at a muzzle velocity of 1800 feet/second because of the recognized blast injury effect of missiles at higher muzzle velocities.[1,2,38] The greater blast effect can inflict additional soft tissue injury locally and can result in arterial contusion for some distance from the local injury site. Soft tissue damage and arterial contusion may influence the success of arterial repair. The preponderance of small arms injuries (44%) reflects the ubiquitous nature of the inexpensive, low velocity handguns available (Table 2).

The mechanism of non-gunshot wounds-penetrating injuries includes stab wounds and major lacerations. In addition, there were two projectile injuries resulting from metal missiles propelled from a lawnmower and a chain saw.

TABLE 1. *Categories of Patients*

Category	No. Patients	Per cent
Acute Repair	46	49
Negative Exploration	35	37
Late Repair	13	14
Total	94	100

Blunt trauma and shotgun injuries were included together as both result in significant and often extensive soft tissue damage. These were further subdivided with regard to presence or absence of associated fractures.

Iatrogenic injuries included only those which required reconstruction in the operating room. There were four injuries resulting from cardiac catheterization and two successfully managed tracheo-innominate artery fistulas.[37] Excluded from cardiac catheterization injuries were those instances where a surgeon was called to perform thrombectomy or to revise lateral arteriorrhaphy in the catheterization laboratory. These four arterial catheterization injuries were the only ones seen during a period in which approximately 900 such procedures were performed. We have seen no acute injuries or late complications of arteriography during this period in which 800 vascular radiographic procedures have been performed.

The site of injury or the major vessel suspected of injury is depicted in Table 3. Each vessel is further subdivided in Figs. 2 and 3 as to the percent of injuries which were subjected to acute repair, negative exploration, or late reconstruction.

Brachial and femoral arteries were injured more frequently than were vessels proximal or distal to these sites.

Acute arterial repair was performed in all proximal vessel injuries (innominate, subclavian, axillary, and iliac). The carotid vessels had the highest incidence of negative explorations (83%), and this reflects our reluctance to manage penetrating wounds of the neck expectantly. Trauma to the forearm and calf arteries (radial-ulnar and tibio-peroneal) was associated with the highest incidence of missed injuries. One-third of radial-ulnar and four-fifths of tibio-peroneal arterial injuries required late reconstruction. There were no negative explorations of these vessels.

Methods of Repair and Results

Group 1—Acute Repair

The methods for acute repair are depicted in Table 4. Resection and end-to-end anastomosis was performed in

TABLE 2. *Mechanism of Injury in 94 Patients*

	No. Patients	Per cent
Low velocity GSW*	41	44
High velocity GSW	17	18
Penetrating-non-GSW	14	15
Blunt or shotgun–without fracture	7	7
Blunt or shotgun–with fracture	9	10
Iatrogenic	6	6
Total	94	100

* Less than 1800 feet/sec muzzle velocity

TABLE 3. *Site of Injury or Suspected Injury in 94 Patients*

Site	No. Patients	Per cent
Carotid	24	26
Innominate-axillary	7	7
Brachial	12	13
Radial-ulnar	6	6
Iliac	3	3
Femoral	29	31
Popliteal	8	9
Tibio-peroneal	5	5
Total	94	100

45%, and autogenous vein graft was used in 31%. Ligation was performed in 5 patients—two radial arteries, one innominate artery (tracheo-innominate artery fistula), one profunda femoris, and one distal tibio-peroneal. The only complication was in a young fireman with extensive soft tissue and bony injury to the foot and ankle which required amputation at a later date.

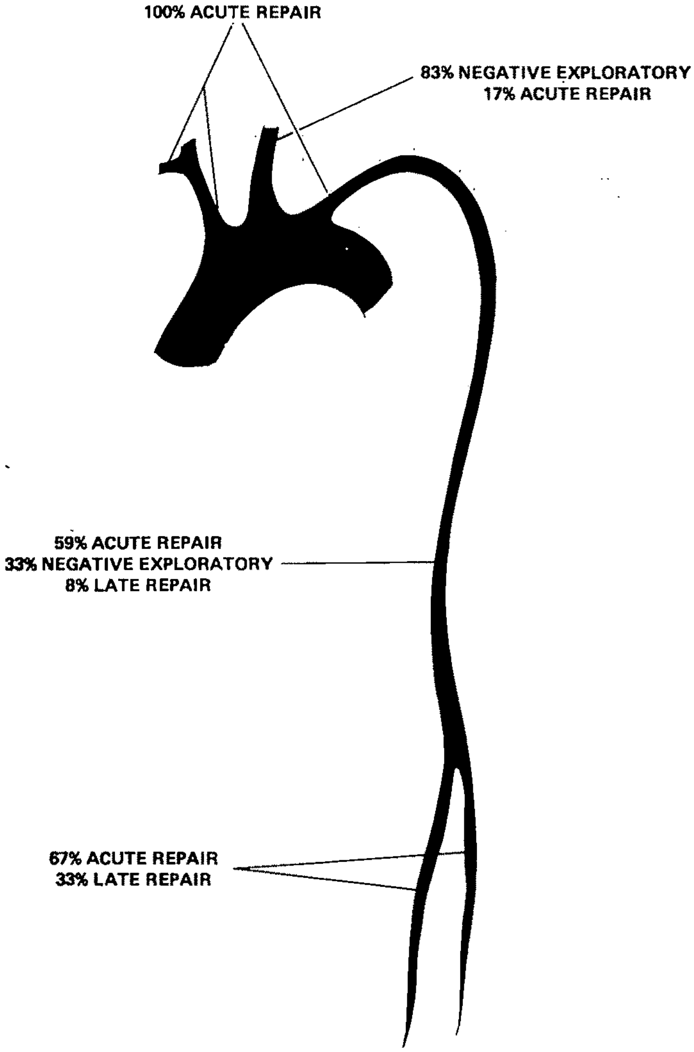

FIG. 2. Management of arterial-injury of neck and upper extremity.

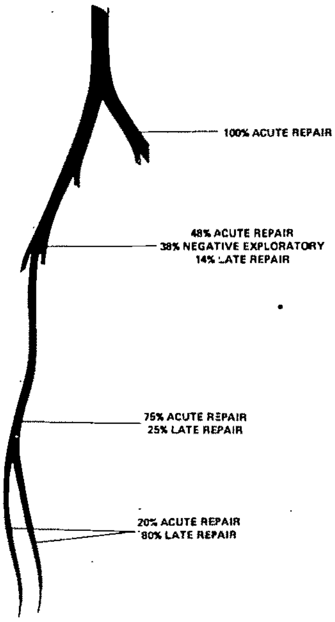

FIG. 3. Management of arterial injury of pelvis and lower extremity.

Table 5 shows the relationship between the harvest site of autogenous donor vein and the results of arterial repair. Results are graded as good for patients with an asymptomatic viable limb without edema, and poor in patients with postoperative edema or in whom amputation was the ultimate outcome. Although the donor vein was taken from the injured extremity in only 5 cases, two resulted in amputation and one in persistent edema. We obtained better results in those patients in whom the donor vein was obtained from a non-injured extremity.

Thirteen major vein injuries were seen in association with the 46 acute arterial injuries (Table 6). There were no amputations and no edema in the group in which the venous injuries were repaired. However, there was a 38% incidence of poor results in the group in which the injured veins were ligated.

There were two deaths in the group of 46 patients undergoing acute repair of arterial injuries, an incidence of 4%. These were the only deaths in this series. One patient with extensive neurological damage on admission died a few hours after control of hemorrhage and repair of a common carotid artery transection. The other death occurred 19 days following repair of a penetrating injury of the superficial femoral artery in a patient with extensive remote injuries. This patient had sustained multiple gunshot wounds to the chest and abdomen with extensive liver injury. The cause of death was endotracheal exsanguination and suffocation from an innominate artery-tracheal fistula.

The failures (amputations) in the acutely reconstructed group are detailed in Table 7. Seven of 46 patients (15%) went on to amputation following acute repair. All 7 patients had either fractures and/or extensive soft tissue damage in addition to the arterial injury.

TABLE 4. *Acute Reconstructions Method of Repair*

Method of Repair	No. Patients	Per cent
Lateral suture	5	10
End–end anastamosis	22	45
Autogenous vein graft	15	31
Ligation	5	10
Evacuation hematoma@ fracture	1	2
Release from compressing bone fragments	1	2
Total	49*	100

* Includes three reoperations.

Group II—Negative Explorations

There were 35 negative explorations for suspected arterial injuries in the 4-year period covered by this review. Suspected carotid injuries accounted for the highest number of negative explorations, followed in order by the femoral and brachial vessels (Figs. 2 and 3).

The complication rate directly related to exploration of the vessel was 8.6%. The complications were all associated with neck explorations and consisted of one wound infection, one unilateral vocal cord paralysis, and one hypertrophic scar which required revision.

Group III—Late Complications of Missed Injuries

The salient features of 13 patients who underwent surgery for late complication of a missed arterial injury are depicted in Table 8. Six patients had an initial investigation which overlooked their arterial injury. The length of delay from injury to definitive reconstruction ranged from one week to 43 years. False aneurysm was the most common late complication (62%) followed by arteriovenous fistula (31%) and claudication (15%). The most striking feature in this group is the finding that 46% of these late reconstructions involved the radial-ulnar or tibio-peroneal vessels.

Although there were no deaths and no limb loss in this group, the results are worse than for acute arterial repair. Four patients (31%) are felt to have results which are less than satisfactory. Two patients have undergone reoperation for persistent A-V fistulae, and one of these still has arteriovenous communication. In addition, two patients had claudication following arterial repair of false aneurysm.

Repair of false aneurysm has been accomplished by either lateral suture, endoaneurysmorrhaphy or interposed vein graft. A-V fistulae have been repaired by either ligation or resection and vein graft. Claudication has been caused by arterial stenosis (Cases 1 and 9, Table 8) and was corrected by resection and vein graft.[23]

TABLE 5. *Results of Autogenous Vein Grafts*

Site of Donor Vein	Performed	Poor Results	Per cent
Ipsilateral	5	3	60
Contralateral	10.	3	30
Total	15	6	40

TABLE 6. *Associated Major Venous Injuries*

Management	No. Patients	Poor Results	Per cent
Vein Repaired	5	0	0
Vein Ligated	8	3	38
Total	13	3	23

Discussion

In this review, we have attempted a critical analysis of three questions: 1) What are the factors contributing to the failure rate of acute arterial repair? 2) What are the implications of a negative exploration of suspected arterial injury, and is a significant percentage of negative exploration justified? 3) Why do large numbers of post-traumatic false aneurysms and A-V fistulae occur as late complications of arterial injury?

An in-hospital amputation rate of 7–15% following elective reconstructive surgery for arteriosclerotic occlusive disease is unacceptable to most vascular surgeons. Why then, should one be complacent with this failure rate following repair of normal vessels in younger patients? The basic tenets for successful arterial repair include: minimal delay in recognition and treatment, generous use of preoperative and intraoperative arteriography, proximal and distal thrombectomy with a balloon tipped catheter, judicious use of heparin, and use of autogenous vein rather than cloth grafts. These are well recognized and have contributed to the improvement of results since World War II. Other important factors are concomitant venous repair, harvest site of autogenous donor graft and the type of treatment for associated fractures and soft tissue injuries.

Experimental work has been reported concerning the role of venous repair in arterial injuries. Barcia and Wright demonstrated a fall in femoral artery flow following venous occlusion, and return of femoral artery flow following release of venous occlusion.[3,40] Hobson, in subsequent studies, showed that if venous occlusion persisted, femoral artery flow would not return to normal before 72 hours.[14] This low femoral artery flow was associated with an increase in peripheral resistance and venous pressure distal to the femoral vein occlusion. Alpha adrenergic blockade and sympathectomy will decrease the fall in femoral artery flow in this experimental setting by decreasing peripheral vascular resistance.[41,42] This work has been reproduced in the primate, whose vascular anatomy in the extremity more closely resembles man.[43]

The mechanism of increased resistance is unclear in these studies. Following venous occlusion, a transitory

TABLE 7. *Failures of Acute Arterial Reconstruction*

Case	Mechanism of Injury	Site of Injury	Delay >6 hr	Ipsilateral Donor Vein	Associated Venous Inj.	Venous Repair	Fasciotomy
1	Blunt + fracture	Popliteal	+	–	–	–	–
2	Blunt + fracture	Popliteal	–	–	–	–	–
3	Blunt + fracture	Common Femoral	–	+	–	–	–
4	Shotgun + fracture	Superficial Femoral	–	+	+	–	Delayed
5	Blunt + fracture	Popliteal	+	–	–	–	Simultaneous
6	Wringer	Brachial	+	–	–	–	Simultaneous
7	Blunt + fracture	Tibio-Pero	–	–	+	–	–
	Per cent		43	29	29	0	43

increase in venous pressure may recruit and distend existing venous channels. However, previous work from this institution indicates that decreased femoral artery flow can follow arterial injury without concomitant venous occlusion.[39] The decreased femoral artery flow and increased peripheral resistance can be reversed by sympathectomy. We have not routinely employed sympathectomy or alpha adrenergic blockade in the management of peripheral arterial injuries. We have, however, used subarachnoid and supraclavicular brachial plexus block when the injury was suitable. In a few instances we have noted subjective improvement in limb warmth and color.

Why does acute repair of arterial injury sometimes fail? The extent and severity of local injury to soft tissue and bone and the coexistence of extensive remote injury in the chest and abdomen may negate or compromise the success of peripheral arterial repair. In patients with multiple injuries including fracture and/or dislocation, limb ischemia may be thought to be due to vascular spasm. The diagnosis of arterial spasm is a frequent trap which is attractive to weary surgeons awakened to care for a trauma victim. Limb ischemia due to arterial spasm is rare. Arterial damage and/or thrombosis must be considered as the causative agent for ischemia, especially in patients with bony or extensive soft tissue injury. Patients with successful resuscitation after thoracoabdominal injuries are vulnerable to delayed complications (false aneurysm, arteriovenous fistula, or limb ischemia) after undiagnosed and/or untreated arterial injuries of the extremities.

Several authors have recommended repair of venous injuries, both isolated and in association with arterial injuries.[21,27,32,35] Our data (Table 6) corroborate that repair of venous injuries associated with arterial injuries results in less postoperative edema and contributes to fewer amputations. In patients with extensive soft tissue, bony and vascular damage, all available veins should be preserved and/or repaired to augment limb salvage. In addition to the theoretical enhancement of arterial flow,[3,14,40–43] maintenance of venous outflow will lessen edema and tissue pressure in closed fascial compartments and improve arterial flow. If autogenous tissues are used in the venous repair, the patency rate is acceptable. If clotting does occur, recanalization may re-establish patency.[32] Because venous outflow is important in the success of arterial repair, it is essential to preserve venous collaterals. In this study (Table 5), use of a donor vein from the injured limb was associated with a greater frequency of edema and amputation than was the use of a

TABLE 8. *Late Arterial Repairs*

Case	Mechanism of Injury	Site of Injury	Time of Delay	Presentation	Initial Invest.*	Results
1	Cardiac cath	Brachial	1 mo	Claudication	None	Good
2	High velocity	Popliteal	2 mo	False Aneur.	None	Good
3	Shotgun (no fract)	Rad/ulnar	1 mo	A-V Fistula	Arteriogram	Fair
4	Low velocity	Tibio-pero	20 yr	False Aneur.	Explored	Good
5	High velocity	Tibio-pero	9 mo	Aneur./Fistula	Explored	Fair
6	Stab-penetration	Radial	1 mo	False Aneur.	Explored	Good
7	Cardiac cath	Femoral	2 wk	False Aneur.	None	Good
8	Low velocity	Tibio-pero	2 mo	A-V Fistula	None	Good
9	Blunt/dislocation	Popliteal	1 wk	Claudication	Arteriogram	Good
10	Low velocity	Femoral	9 wk	False Aneur.	None	Fair
11	Low velocity	Femoral	43 yr	False Aneur.	None	Fair
12	High velocity	Tibio-pero	3 wk	A-V Fistula	Arteriogram	Good
13	Low velocity	Femoral	8 mos	False Aneur.	None	Good

* Exploration or arteriography.

vein from the uninjured limb. The use of an ipsilateral vein graft is especially hazardous in patients with extensive soft tissue, bony, and vascular injury.

We have had no experience with the use of porcine skin grafts to cover exposed vein grafts in patients with extensive skin and soft tissue loss.[19]

When edema impairs limb blood flow, fasciotomy should be considered. Fibulectomy-fasciotomy has salvaged limbs with extreme edema and impaired blood flow.[10,20] In the upper extremity we have used long fasciotomies and have avoided short fasciotomies through limited skin incisions.

The association of fractures with arterial injuries as a determinant in limb survival cannot be over emphasized. All but one amputation in our patients occurred in association with fractures (Table 7). It is doubtful that the presence of a fracture per se has a detrimental influence on the outcome of arterial repair. Usually there is an element of delay in reconstruction either preoperatively or intraoperatively while orthopedic manipulations are carried out.[4] In addition, injuries with sufficient force to cause fractures can result in associated soft tissue and venous injury which may have a negative bearing on the eventual outcome. There is no clear answer to the question of internal versus external stabilization of fractures. Internal fixation has been recommended by some,[25,34] but the Vietnam experience and subsequent studies suggest the use of external stabilization.[5,6,28,29]

The question of negative exploration for suspected injury is closely related to that of the role of arteriography in the management of arterial trauma. Diagnostic confirmatory arteriography delays acute repair of obvious arterial injuries, and is not indicated. Equivocal arterial injury is the most frequent indication for arteriography.[33] Arterial injury may be present despite a normal arteriogram.[17,18,33] We had 23% false negative arteriograms in patients with late complications (false aneurysms and A-V fistulae). We feel that direct exposure and examination of a vessel suspected of injury is more accurate than arteriography. Intraoperative arteriography can be used to determine presence or absence of other injuries, peripheral thrombus, and adequacy of repair. Precise arteriography is mandatory prior to definitive repair of traumatic A-V fistulae or false aneurysms. These lesions may be multiple and easily overlooked resulting in incomplete repair.

Negative exploration carries an acceptable morbidity rate when compared to the complications of missed arterial injury. Surgeons should not be any more reticent or apologetic about negative exploration for equivocal arterial injury than they are in performing thoracotomy for a possibly malignant pulmonary lesion.

Late complications of arterial injuries—false aneurysms, arteriovenous fistulae, and ischemia—continue to be seen by the vascular surgeon.[11,13,16,22,31] Analysis of our patients reveals that the greatest percentage of complications (46%) occurs in those individuals with radial-ulnar and tibio-peroneal injury. Arterial injury below the elbow and knee is oftentimes watched until, or unless, obvious hemorrhage or ischemia appears. Arteriography and/or early exploration of these areas may lessen these complications. Recent technical advances allow surgical reconstruction of small vessels, and suggest aggressive rather than expectant treatment in these sites. We concur with a recent report that advises exploration of these vessels with revascularization when possible, and ligation where it is not.[17] Reconstruction of traumatic aneurysms and arteriovenous fistulae is more demanding than is acute repair of arterial injury.

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DISCUSSION

DR. DAVID M. CONKLE (Nashville, Tennessee): I thoroughly enjoyed Dr. Campbell's presentation, and I agree with his conclusions regarding the correlation of the type of injury and the success of salvage, and the need for concomitant venous repair, whenever possible.

(Slide) Since January 1, 1959, we have seen 34 patients with popliteal artery injuries. All 34 patients underwent operative exploration following arteriography. There were no operative or hospital deaths.

(Slide) In breaking down our experience, we also found our salvage rate to be related to the type of injury incurred. In the 13 patients with penetrating injuries, successful reconstruction was achieved in 85% of the patients. In the 21 patients who experienced blunt trauma, our salvage rate fell to 52%. The overall success rate was 62%.

(Slide) In correlating the salvage rate with associated injuries, primarily in those who experienced blunt trauma, our data again backs Dr. Campbell's, in that it points out the negative influence that massive trauma has on successful salvage.

Our mode of treatment has been primarily with reversed saphenous vein segments taken from the noninvolved leg. If sufficient length is present to permit the anastomosis to be made without tension, end-to-end anastomosis is employed.

I'd likewise agree that all vessels should be explored and looked at very carefully, because minor procedures such as thrombectomy ordinarily lead to failure because a small intimal tear is overlooked.

We likewise employ fasciotomy in the postoperative patient who demonstrates evidence of decreased perfusion and compression in the compartment distal to the repair.

In closing, I would like to ask Dr. Campbell if fasciotomy was employed in any of his patients, and if he felt that it affected his results.

DR. FRANK C. SPENCER (New York, New York): Regarding diagnosis, as the authors quite properly emphasize, a liberal index of suspicion is especially important. Any wound in proximity to a major artery should be regarded as a potential arterial injury, regardless of the absence of clinical signs of arterial injury. An arterial injury can be excluded with certainty only by an arteriogram or operative exploration.

The long-term goal with arterial injuries, of course, is to decrease the amputation rate. In this series, like other recent reports, the overall amputation rate was 10–12%. Future improvement will probably come in two areas. First is the more extensive teaching of principles which have been enunciated several times. The time interval between arterial injury and restoration of flow following arterial repair is crucial. If the objective of restoring blood flow within six to eight hours after injury is considered of paramount importance, arranging priorities accordingly, decisions such as preoperative angiography, priority of treatment of multiple injuries and similar considerations can be made accordingly. A retrospective analysis of many amputations finds that the basic problem was simply that arterial repair was not accomplished within six to eight hours for a variety of reasons, partly because extreme emphasis was not placed on this point.

Another future improvement in therapy can probably be achieved with the frequent use of operative angiography. The two most common failures of arterial repair are either an inadequate vascular repair or inadequate removal of thrombus from the distal arterial tree with a Fogarty catheter. Both mishaps can be promptly detected with operative arteriography and treated accordingly.

To repeat, much of the failure to lower the amputation rate with arterial injuries is not inadequate knowledge but inadequate teaching. One approach is for each institution to have an annual or semi-annual review of experiences with arterial injuries, determining whether the previously mentioned principles of arterial repair within six to eight hours and operative arteriography are being properly emphasized.

Poor results are still obtained in almost all institutions with complex injuries of the popliteal artery in association with extensive destruction of soft tissues and fracture of the femur. In previous discussions I have suggested that in many such patients primary attempts at arterial repair in such instances should be abandoned because of the high failure rate in the absence of adequate soft tissue to cover the site of arterial reconstruction. An extra-anatomic approach, perhaps with a vein homograft, which has been widely used at our institution, could be initially employed. The vein homograft works surprisingly well for one to two years. Hence, with an extra-anatomic approach, blood flow can be re-established between the proximal artery and the distal leg.

Once blood flow was re-established, the operative wound can be left open and the problem of soft tissue coverage completed at a later date. Once soft tissue coverage is accomplished, elective repair of the popliteal artery can be done at a later time. I think this deliberate two-stage approach merits important consideration, because the majority of severe injuries of the popliteal artery, as with a shotgun, associated with fracture of the femur, loss of soft tissue and concomitant popliteal and saphenous vein injuries, attempts at direct repair either fail immediately or subsequently because of infection and disruption of the anastomosis from loss of soft tissue.

Finally, I heartily agree with the authors that arterial spasm is a dangerous myth that has resulted in erroneous treatment and subsequent amputation in several extremities. In the past 15 years I have seen only one or two instances of genuine spasm with the possible exception of spasm in the brachial artery following manipulation of a catheter during cardiac catheterization.

In closing, my question is: "What were the major causes of the amputations?" Were these due to delay in accomplishing arterial repair within six to eight hours or to failures of repair? Or, were they due to inadequate soft tissue coverage with subsequent infection and arterial disruption?

As the authors quite properly emphasize, elective peripheral vascular operations with an amputation rate of 10% would be considered unacceptable by almost everyone and yet this result remains at about this level with several reports with arterial injuries over the past decade. I am quite confident that members of this organization can do much better.

Dr. Lewis Flint (Louisville, Kentucky): The comments that I would like to make will be restricted to one category of vascular injury, and that is in the base of the neck.

(Slide) We conducted a retrospective review at the Parkland Hospital in Dallas, and looked at 199 proven vascular injuries at the base of the neck in 146 patients. We tried to reexamine in this series the validity of the "exploration for proximity" concept. Thirty-two per cent of these patients have proven arterial or venous injuries, even though the signs of vascular injury were absent. The definition of a proximity exploration is in the upper right-hand corner of this slide.

We were happy to see a very low mortality in this series, although in our base-of-the-neck injuries one bothersome cause of death is seen on the next slide; that cause is intraoperative hemorrhage. We feel that the key to avoidance of this particular problem is adequate exposure and proximal control prior to entering the hematoma in the area of the injury.

We were struck by two other things in this series; the very low morbidity in patients who had negative explorations of their vessels, and the fact that although we tried to detect complications of missed injuries, such as false aneurysm, we were unable to find any over a two-year period, if the patient was first seen at Parkland and explored for proximity.

I would like to ask Dr. Burnett if they have examined the results of negative explorations in their institution and also noted a low morbidity.

Dr. Robert P. McBurney (Memphis): I'd like to emphasize the iatrogenic arterial injuries; specifically, those which occur as a result of arteriographic procedures. I presume his 6% probably represents that type of injury.

This is extremely important to us all, because the patient goes down to x-ray with a reasonably good arm or leg circulation and if he comes back to his room with a cold, pale hand or foot you can imagine who get the blame for it if the result is not good.

At the Baptist Hospital we have an extraordinarily large neurosurgical as well as vascular service, and we do about 2000 arteriographic procedures per year, a thousand of which are brachial arteriograms. About three years ago, two of my colleagues and I reviewed some 4000 of these brachial arteriograms and found 22 cases where there was either thrombosis or, in two cases false aneurysm formation following brachial arteriograms.

Now, if this is recognized and properly treated, the results should be good; but this is not always the case, and, again, procrastination and the spasm idea probably is the thing that prevents immediate or proper treatment.

(Slide) That treatment can be effective, if properly applied, is illustrated by this one case, which I think is probably the longest brachial radial-ulnar thrombus I have ever seen. It was extracted in one of the cases which I had the opportunity to see. You can see the thrombus from the superficial brachial, and both radial and ulnar arteries.

This was a case where there was some procrastination. The patient was not operated on until 24 hours after arteriograms but even at that time it was possible to extract these thrombi and get a good result.

(Slide) This is just the procedure that I like to use. The brachial artery is small, and following the extraction of the thrombus, I don't like to do primary repair, because usually the intima has been damaged, so I do an onlay vein graft.

(Slide) That false aneurysm can occur is demonstrated by this patient, a young man who had a brachial arteriogram, and this developed about three months later. It was first thought to be a hematoma, but on later examination it pulsated.

(Slide) At operation it was very simple to repair. Once the false aneurysm was dissected away, we got down to a small hole which only required one stitch to close.

(Slide) In some of these patients where the hand has remained viable, but the patient later has claudication and symptoms of arterial insufficiency, a bypass vein graft can be done, as illustrated by this case.

That this is certainly important to everyone has been emphasized to me just this last year, when I was asked to be consultant to defendants' lawyers in two cases, one where part of a hand was lost as a result of arteriograms and improper recognition and treatment, and another case where a leg was lost. So I would like to emphasize that this can occur. It does occur in about a half of one per cent of arteriographic procedures, in our experience, and it certainly needs to be recognized for the patient's safety and protection, as well as that of the physician.

Dr. H. Harlan Stone (Atlanta): (Slide) One of the problems frequently encountered in the management of trauma is an individual with the wounding object still in place. This man, you will note, still has the knife pushed up to the hilt in the middle of his back. There are two ways to look at such. We as surgeons would say: "He should be carried to the operating room, and then the knife could be pulled out." However, in order to do that, it would be preferred to have the patient anesthetized.

(Slide) The anesthesiologist, on the other hand, looks at the patient from a little different angle and worries more about the airway. This conflict of interest is particularly compounded in the inebriated patient who cannot cooperate.

To solve this dilemma, these patients are taken to the operating room and are given ketamine. The effect of the drug is similar to what would result from administration of a very potent tranquilizing agent and does not demand that an airway already be established. The knife or other object can then be pulled out once the operating room is in readiness for definitive surgery in cases where the blade happened to have hit a vital organ or some major vascular structure.

DR. HUGH F. BURNETT (Closing discussion): To summarize our findings briefly: The majority of failed acute arterial repairs are those associated with extensive soft tissue and bony damage. Repair of associated venous injury appears to improve limb salvage rate, and decreases disability resulting from edema. Our data indicate that autogenous vein grafts should be harvested from a non-injured extremity.

In this series of patients, late complications of missed arterial injuries, false aneurysm, and A-V fistula occurred most often in the vessels below the elbow and the knee. These were the vessels least often subjected to exploration for potential arterial injury. An aggressive investigative and reconstructive approach toward suspected or proved arterial injury should be continued.

Dr. Conkle has reported a 65% success rate with 34 popliteal injuries—an admirable result. We are pleased to see that his results support our advocation of repair of associated venous injuries and the use of saphenous vein grafts from the uninvolved leg.

With regard to his question concerning fasciotomy, we employed fasciotomy in three cases, two acutely—that is, two at the time of the original procedure—and one later, as edema began to impair arterial blood flow. We have not found it to be a determinant of success, and this is probably related to our not employing it often enough nor early enough.

It should also be noted here that fibulectomy-fasciotomy is the one type of fasciotomy which in the lower extremity will open all four compartments, and we have not hesitated to use this type when indicated.

We appreciate Dr. Spencer's kind remarks and his questions. Our causes of limb loss are correlated most closely with associated fractures and extensive soft tissue injury, associated venous injury, failure to repair associated venous injuries, use of an ipsilateral donor vein, and delay in recognition of the injury. Delay was implicated in four of the seven amputations in this series, and there was extensive soft tissue damage in each. His point is well taken in that there are probably some of these limbs in which heroic measures are simply salvaging a useless limb, and amputation may well be considered earlier.

His point regarding biennial review of results with regard to arterial injuries is well taken, and we will look forward to employing this.

Dr. Flint's remarks concerning the Parkland experience we enjoyed very much, particularly with regard to his data concerning cervical injuries. We have an 83% negative exploration rate in the neck in our series, and feel that this simply reflects our reluctance to treat penetrating wounds of the neck expectantly. We have taken an aggressive approach to these wounds and have found that we have an 8.6% complication rate, all of these being minor complications. We will continue to use this approach.

With regard to root of the neck injuries or thoracic outlet injuries, intraoperative hemorrhage at the time of exploration is certainly a disaster and a pitfall to be avoided. We have likewise had this experience, and have since advocated liberal use of median sternotomy and proximal control of the major vessels whenever we have felt that it was indicated.

With regard to Dr. McBurney's question, we have seen no late arterial injuries resulting from arteriography. Our six iatrogenic injuries included four resulting from cardiac catheterization and two from successfully managed tracheoinnominate artery fistulas. The site of injury in those reconstructions following cardiac catheterizations were three in the brachial artery and one in the femoral artery. All presented as thrombosis or stenosis with claudication. Over the four year period which this series encompassed, this includes about 1,000 arteriograms and 1,000 cardiac catheterizations.

I thank Dr. Stone for bringing a difficult problem to our attention, and will certainly employ his use of Ketamine in extracting these objects left in place under anesthesia in the Operating Room.

Tibial and Peroneal Bypass in Severe Occlusive Disease of the Lower Extremities

WILLIAM H. EDWARDS, M.D., ROSS S. WRIGHT, M.D.

Symptomatic arteriosclerotic occlusive disease involving the femoral and proximal popliteal arteries is currently best treated by reversed autogenous saphenous vein bypass graft. Severe occlusive disease frequently includes the popliteal and/or origin of the trifurcation vessels with reconstitution of one or more of the vessels in the lower leg. We have used distal bypass 97 times in 90 patients during the past decade. There was only one postoperative death in the series in spite of the advanced age and concurrent disease in the majority of the patients. Our indications for operation continue to be relief of pain or salvage of an extremity. We rely on high quality preoperative angiograms for selection of vessels to receive the bypass. The posterior tibial artery was used in 63 of the cases, while the anterior tibial and peroneal were used in 24 and 10 cases, respectively. There were 11 immediate inhospital failures in this series of 97 cases requiring amputation in five. Three additional patients had amputations during the ensuing several months. Of the 85 grafts functioning at the time of discharge from the hospital, 16 or (18.8%) failed during the first years. Grafts that remained patent for one year have a high incidence of long term patency which is in keeping with other reported series.

THE REVERSED autogenous saphenous vein is the best tubular structure available to effectively bypass arteriosclerotic occlusive disease of the lower extremities. The patient whose chief complaint is calf claudication after walking probably will have superficial femoral occlusion with reconstitution of the arterial system at the popliteal level. In a high percentage of patients, however, the occlusive disease is more severe and the symptoms are rest pain or impending gangrene with the occlusion extending below the popliteal segment. It is in these patients that the feasibility of distal bypass has been shown to be effective in salvage of limb and to relieve pain.[6,9,13]

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Nashville, Tennessee

Ninety patients with superficial femoral and popliteal artery occlusion, but with patency in the tibial or peroneal arteries form the basis for this report. We have used a distal bypass as a safe and effective technique for the relief of rest pain and the salvage of extremities, and have continued to attempt to restore flow directly to patent distal vessels by combinations of bypass grafts.

Materials and Techniques

Since 1966, we have performed a distal bypass in patients whose presenting symptoms indicated severe ischemia and in whom there was a patent distal artery. Sixteen patients (16%) had symptoms of claudication alone which was severe enough for us to feel that a distal bypass was indicated. Thirty-five patients (36%) had rest pain while 43 (44%) had ulcerative changes of the skin of the foot or ankle. There was one instance of an acute femoral occlusion requiring a distal bypass to restore flow and two thrombosed popliteal aneurysms in which there was patency of the distal vessel well below the trifurcation. The youngest patient in this series was 43 years old with the oldest being 96. Males outnumbered females 67 to 23.

Improvement in the radiographic equipment available now makes it possible to determine with a high degree of accuracy the patency of vessels of the lower leg and foot. To achieve this, we feel that a percutaneous needle femoral arterial injection is superior to a catheter injection at the aortic level. The delivery of the entire

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Presented at the Annual Meeting of the Southern Surgical Association, December 8–10, 1975, The Homestead, Hot Springs, Virginia.

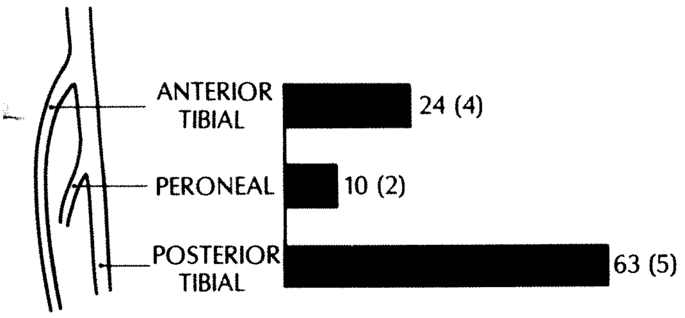


FIG. 1. When technically possible, the posterior tibial is the artery chosen to receive the distal bypass (the numbers in parentheses indicate failures).

bolus of dye into the femoral artery does not decrease the dilution and increases the probability of opacification of the vessels of the lower leg. We therefore prefer to perform bilateral femoral arteriogram simultaneously, obtaining 4 to 6 sets of films of the entire lower extremity visualizing the circulation into the foot. With this technique, we are certain that patent distal arteries will be demonstrated.

Whenever possible, the posterior tibial artery is the vessel of choice, but if for any reason it is felt to be inadequate, the anterior tibial or peroneal artery is used for the distal bypass. The peroneal offers the most technical difficulty and continues to be our last choice if either of the other vessels is available. We do not hesitate to approach the posterior tibial or anterior tibial (dorsalis pedis) at the ankle. Either artery is easily exposed at this level, but at the same time, the surgeon must be certain he has an adequate length of saphenous vein available. Since the vein contracts on removal, it is essential to have several centimeters of extra length to insure the proper tension at suture lines.

We prefer to perform the proximal anastomosis at the common femoral artery. Although the proximal superficial femoral artery may be patent, there is a high incidence of disease present at its origin and we feel that to bring the graft off such a vessel might give inadequate inflow to the bypass.

If our distal anastomosis is to the posterior tibial or peroneal artery, we approach the vessel from whatever point seems best along the medial aspect of the lower leg. The posterior tibial artery offers no difficulty in exposure as it courses down the leg beneath the soleus muscle. The peroneal, deeper in the leg, requires a much more extensive dissection for exposure. We expose the anterior tibial artery with a lateral incision and then have the choice of bringing the bypass along the medial or lateral aspect of the thigh.

Autogenous saphenous tissue is our first choice for a distal bypass. If possible, we use the vein in the involved leg, but do not hesitate to use the contralateral vein, if necessary. If an ulcerated lesion or gangrenous toe is present on the lower leg or foot, thrombosis of the saphenous vein may have occurred. We therefore prepare both lower extremities at the time of operation. If the saphenous vein is inadequate or has previously been used, composites of cephalic veins and short Dacron bypass are constructed to bridge the length of occlusion. The Sparks Mandril has been used on one occasion while homologous veins were used on two occasions. At the present time, we are continuing to explore the use of homologous veins, but would hope that a more ideal material might become available.

Results

To justify a surgical procedure, it must be shown that the operation has an acceptable morbidity and mortality and will lead to relief of symptoms in a high percentage of cases. Restoration of arterial flow offers the best opportunity for relief of pain and healing of ischemic ulcers in advanced distal occlusive disease. It has been our approach during the past decade that if we could restore flow with a distal bypass and salvage an extremity, the operation should be made available to the patient.

In this series of 90 patients in whom 97 bypass procedures were performed, there was one hospital death. One patient suffered a postoperative hemiparesis and survived. There were, in addition, other commonly encountered postoperative complications such as urinary tract infections, pneumonia, and wound hematomas. Wound infections occurred in several patients with open lesions on the lower extremities; one infection led to thrombosis of the bypass two weeks after operation.

In the 97 bypasses, the three trifurcation vessels were all used (Fig. 1); the anterior tibial 24 times (24.7%); the posterior tibial 63 times (65%), and the peroneal 10 times

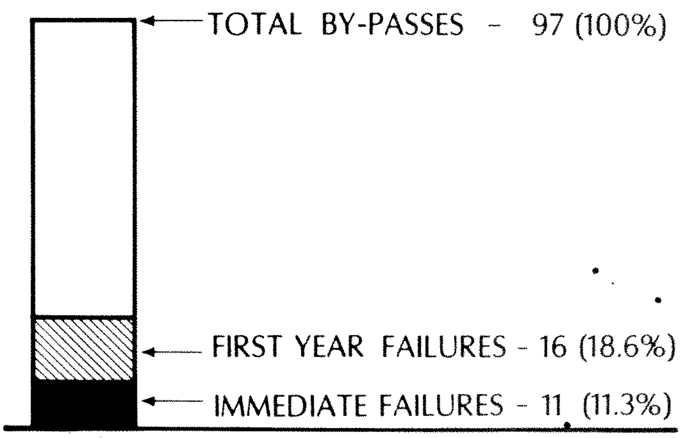


FIG. 2. Those bypass grafts that remain patent for one year have a high incidence of continued patency.

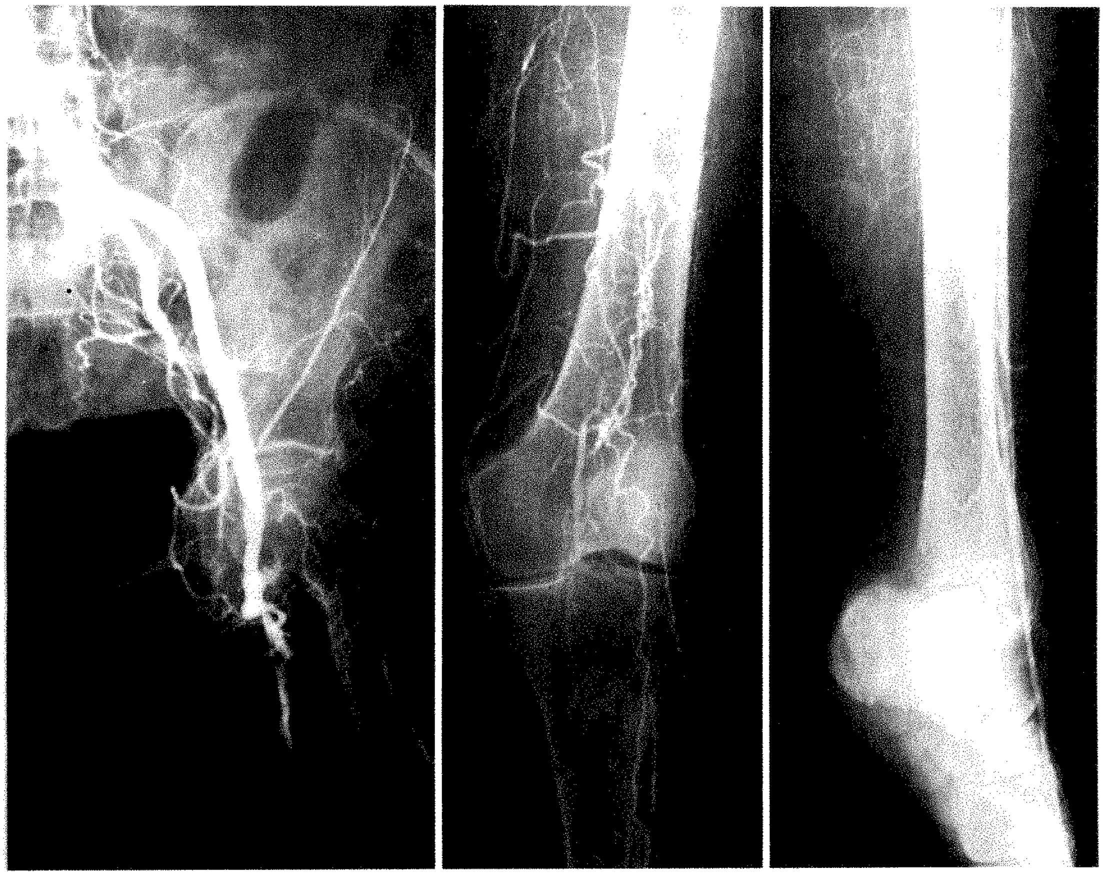


FIG. 3a. Extensive superficial femoral occlusion with a short isolated popliteal and a large patent anterior tibial artery.

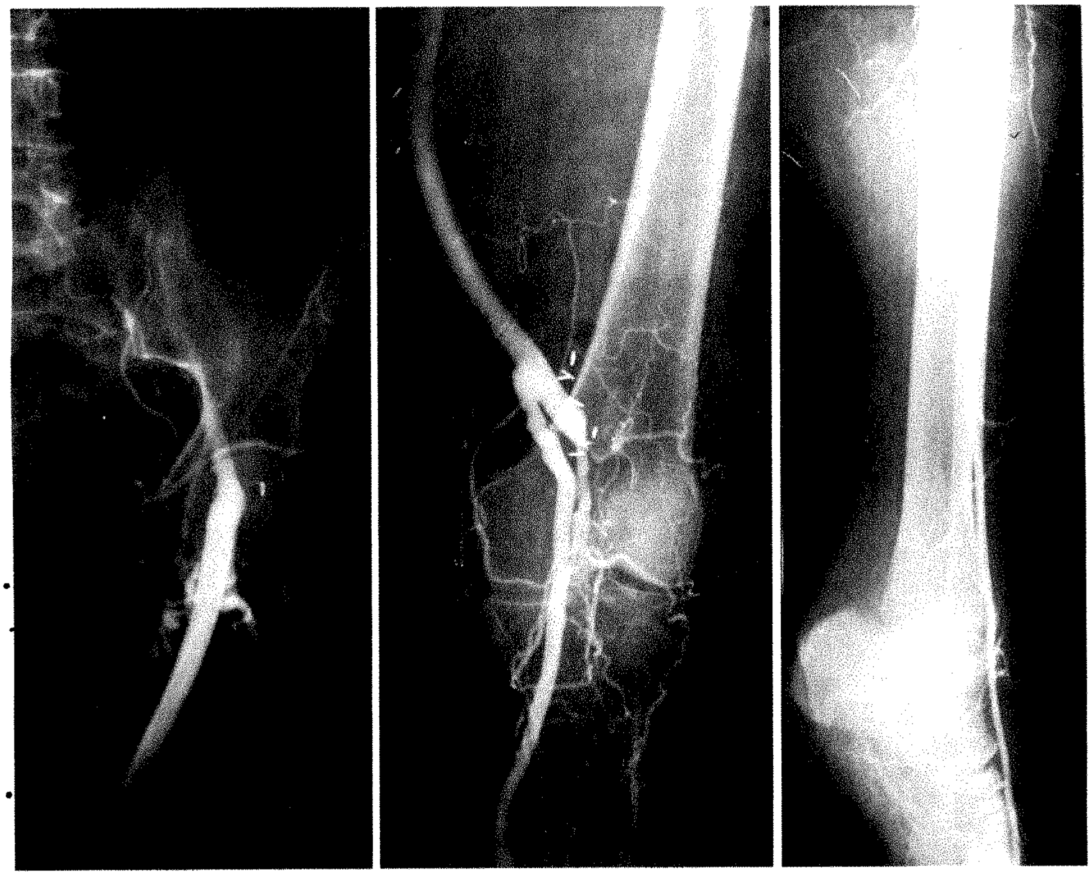


FIG. 3b. Postoperative arteriogram demonstrates the Dacron bypass into the isolated segment with the vein bypass to the anterior tibial artery.

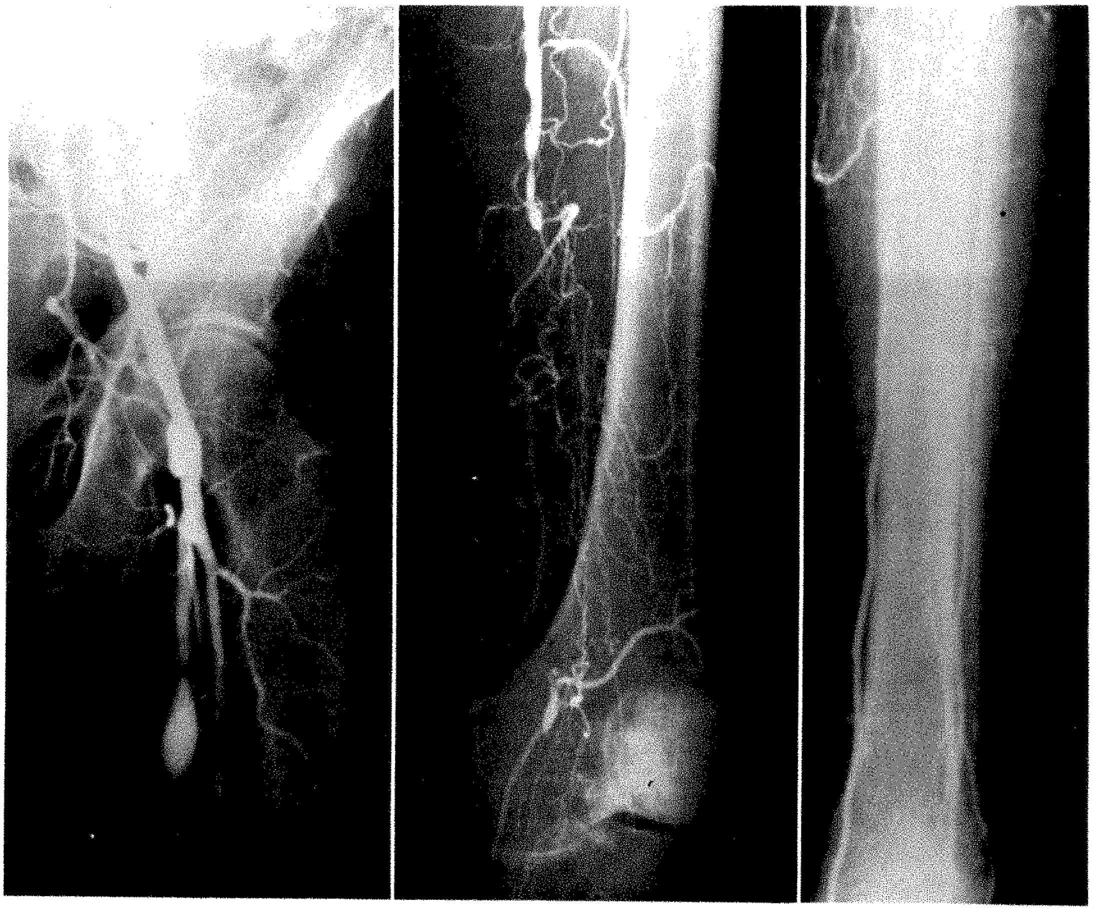


FIG. 4a. There is extensive disease in the superficial femoral with occlusion in the mid-thigh. A 1.5 cm segment of popliteal remains patent with a large posterior tibial and smaller anterior tibial present in the leg.

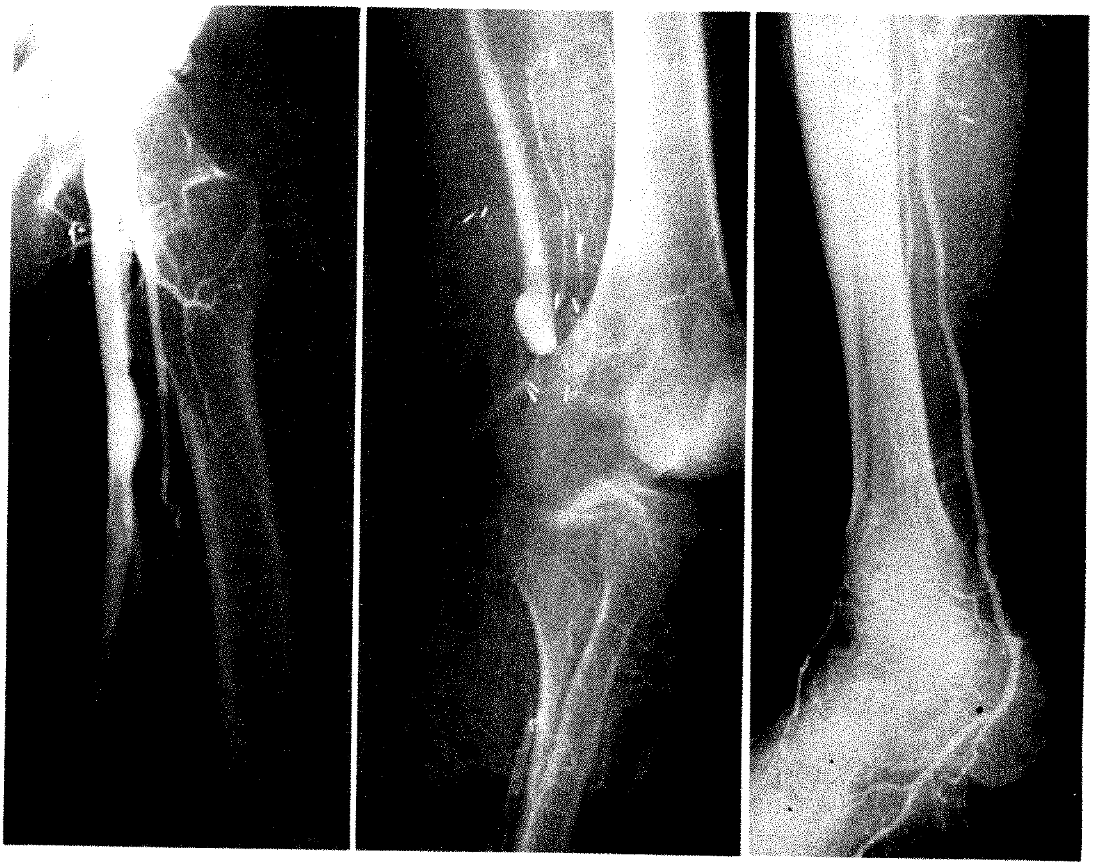


FIG. 4b. Arteriogram demonstrates patency into the posterior tibial with very little filling of the isolated popliteal segment.

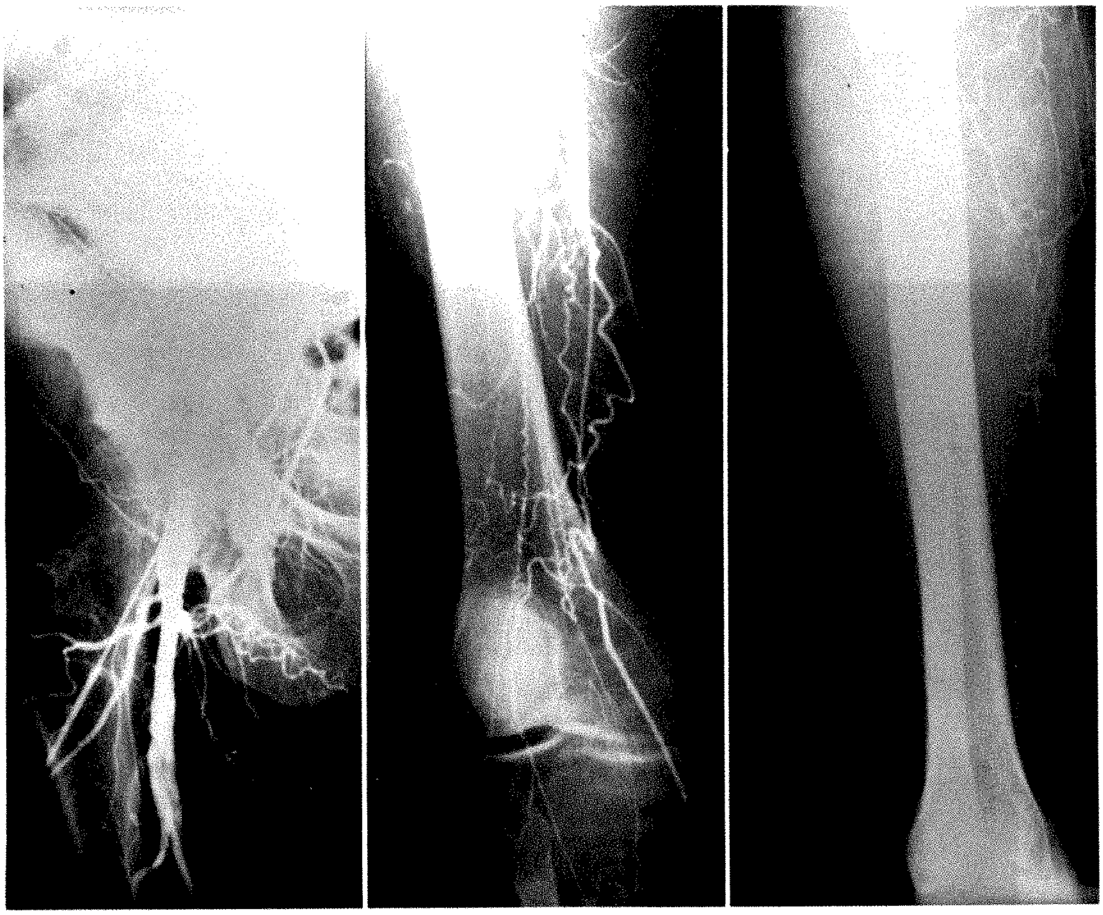


FIG. 5a. Filling defect in the common femoral artery is just beneath the needle shaft with occlusion of the distal superficial femoral and popliteal and poor filling of the distal vessels with little collateral filling.

(10.3%). Failure occurred four times in the anterior tibial (16.7%); five times in the posterior tibial (8%), and twice in the peroneal (20%). Thus, there were 11 immediate failures. Amputation was necessary in five of these failures during that hospitalization while the remaining patients had viable extremities. Three additional amputations were necessary during the ensuing 4 months, leaving 3 patients with failures of their grafts that did not require amputation. Since we feel that distal patency justifies attempted bypass, we obviously felt that these failures had a chance for success. Continued experience, however, gives us a better insight into those that will remain patent. Experience also allows us to correct the technical difficulties that have led to some failures.

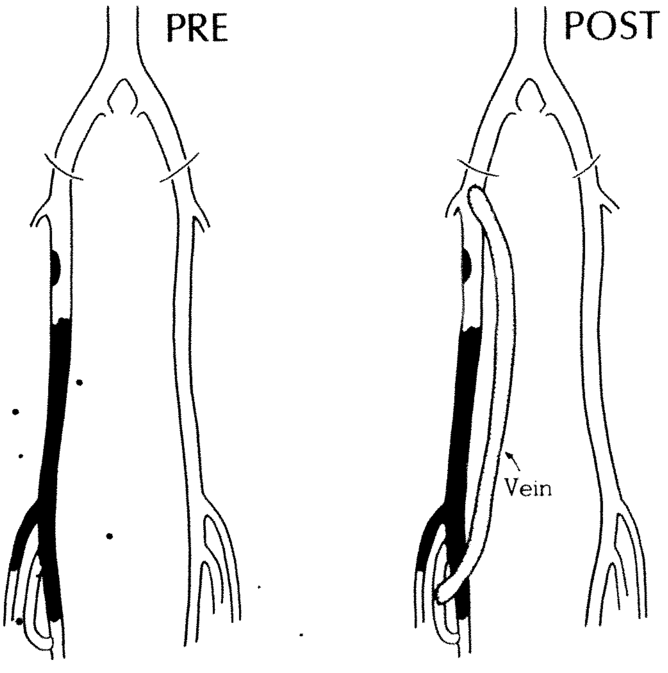


Fig. 5b. Drawing of Fig. 5a.

Of the 85 grafts functioning at the time of discharge from the hospital, 16 (18.8%) (Fig. 2), failed during the first year. In this group of 16 failures, there were 6 deaths and 4 patients required amputation.

Our experience parallels other reported series[3,11] on the long term patency of bypasses. Only six bypass occlusions occurred in those that remained patent for one year.

Types of Reconstruction

In order to achieve increased blood flow to an ischemic extremity, various types of arterial reconstruction have been described depending on the location of the occlusive lesion. In those situations in which stenosis is present in the profunda femoris, profundoplasty has been recommended as the ideal procedure.[10,12] With an isolated popliteal segment demonstrated by arteriogram, this is

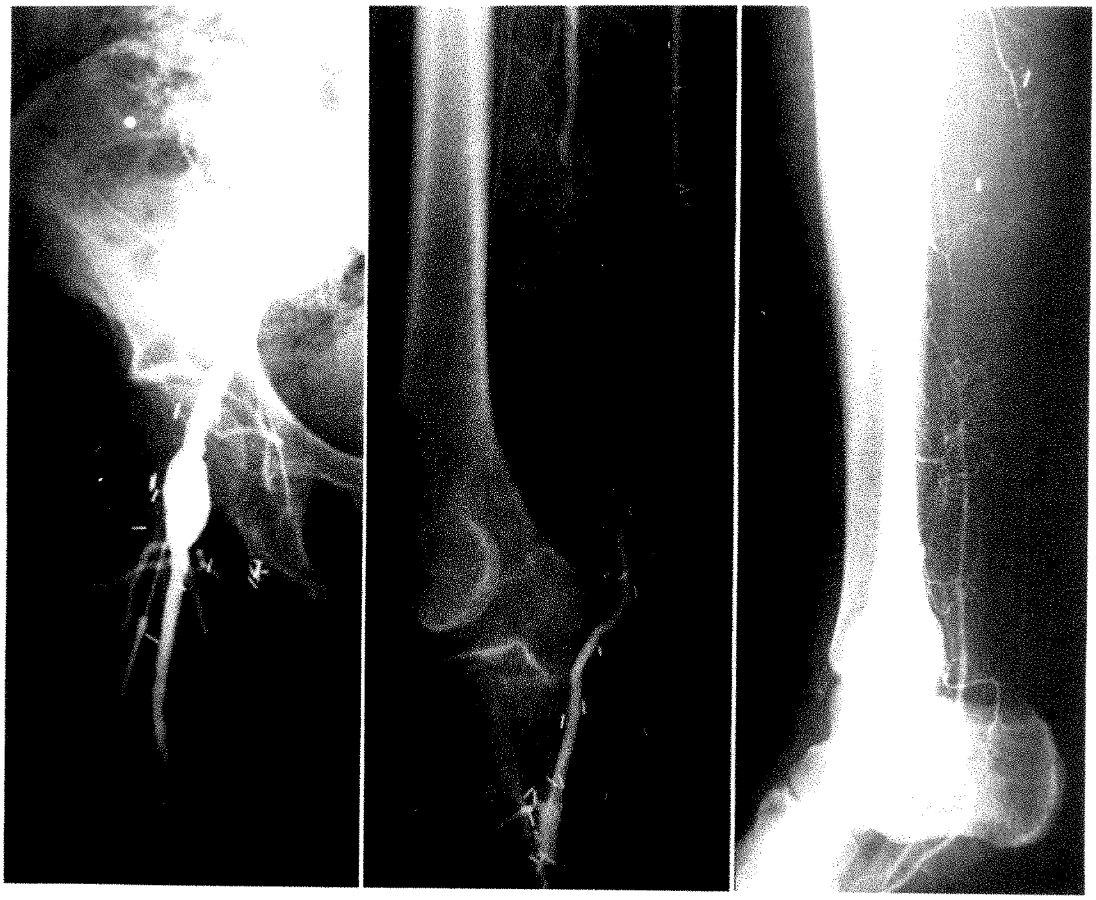


FIG. 5c. The distal anastomosis of the vein bypass is to the peroneal which in turn supplies the posterior tibial in the lower leg.

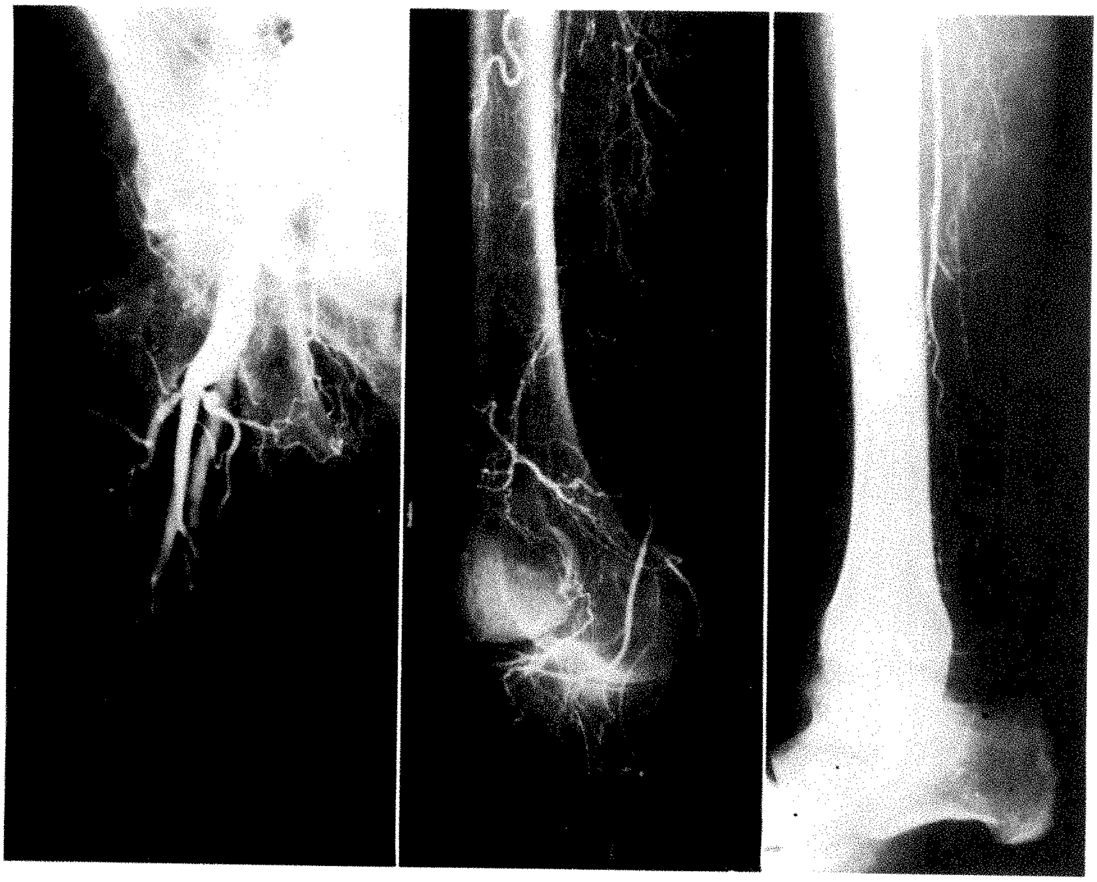
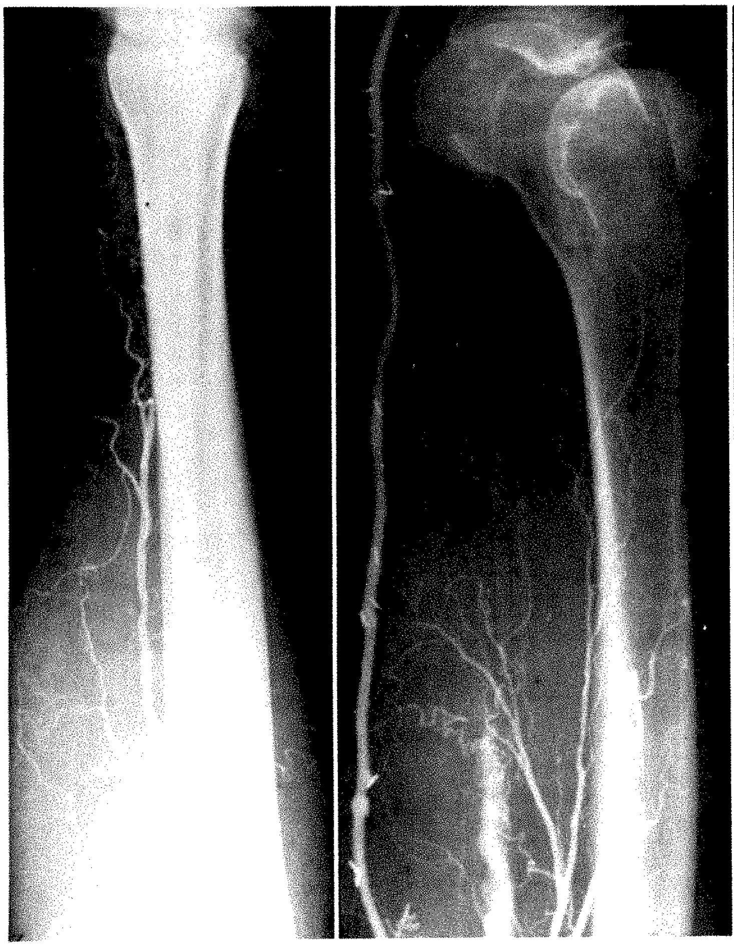


FIG. 6a. Preoperative arteriogram demonstrates the extensive occlusive process from upper thigh to mid-calf with filling of the peroneal distally.



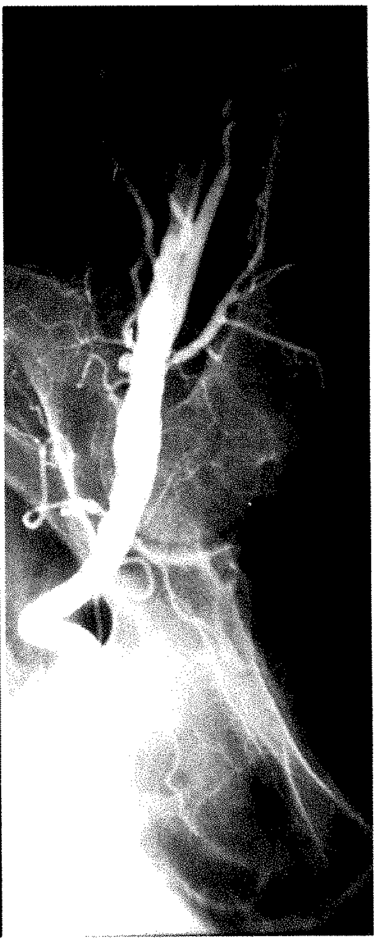


FIG. 6b. The vein bypass extends distally to the peroneal artery.

sometimes chosen as the vessel to receive the bypass.[2] Lastly, a tibial or peroneal bypass may be chosen to restore flow.

This series of 97 bypasses was achieved with various combinations of materials as well as various sites of origin for the proximal anastomosis. The distal anastomoses, however, were all performed in the tibial or peroneal arteries.

Fig. 3a is the preoperative arteriogram in an 80-year-old woman with an ulcerated lesion of the foot. A saphenous vein bypass to the patent anterior tibial artery was the preoperative plan. At operation, the vein was inadequate, necessitating a composite of dacron to the short isolated popliteal segment, and a short venous segment across the knee to the anterior tibial (Fig. 3b).

A similar composite bypass was constructed in a 67-year-old man in whom a femoro-popliteal bypass had been performed two years previously but had failed. A short segment of the popliteal artery was patent, was extensive superficial femoral and distal popliteal occlusion (Fig. 4a). The postoperative arteriogram (Fig. 4b) shows composite bypass into the isolated popliteal segment and the vein bypass to the posterior tibial artery.

When possible, a long saphenous vein is used as the bypass. Fig. 5a shows an arteriogram with extensive superficial femoral and popliteal occlusive disease but with patency of the peroneal artery (Fig. 5b). The postoperative arteriogram (Fig. 5c) shows the distal filling with the patent vein bypass. A similar long vein bypass was performed for thrombosis of a popliteal aneurysm (Fig. 6a). The peroneal artery in the leg is seen to be large in the upper portion, but much smaller at the ankle level. The vein bypass (Fig. 6b) is seen functioning.

Comments

A reconstructive bypass procedure for far advanced occlusive disease of the lower extremities is a safe effective method for the relief of pain and to allow the healing of ischemic ulcers. Most vascular surgeons do not share the viewpoint expressed by Wylie[14] advising early amputation rather than restoration of blood flow. Limbs will be lost in attempts to reconstruct badly diseased arteries in elderly patients with other disease conditions. It has been shown, however, that mortality and morbidity are low and that a senior citizen who has been active is more likely to survive if the lower extremities are not amputated.

We have been impressed with the lack of arteriosclerosis in many of the small distal vessels to which distal bypasses are attached. It seemed as if these vessels with proximal occlusion have been spared the ravages of the disease. It is much the same phenomenon that has been observed in patients with complete aortic occlusion and no evidence of distal occlusive disease. We do not hestitate to use a vessel regardless of the degree of disease if there is an adequate lumen and distal patency.

We feel that adequate arteriographic evaluation of the lower arterial bed is essential in planning the operative care of the patient. We prefer to achieve this with preoperative arteriograms which show us all patent vessels and the patency of the pedal arch. It is essential that the physical findings of the involved extremity and the arteriographic findings be closely correlated. If we have not achieved this with our preoperative arteriograms, we then perform an intraoperative arteriogram to give us this information.

We have used several techniques in our approach to the distal vessel. For several years we preferred the technique described by Garrett for a common femoral to anterior tibial bypass. This has proven satifactory, but we have more recently used the medial approach passing the graft through the interosseous membrane and believe that this might be a better technical method. We have, on one occasion, used the tibial tunnel technique as described by Dillihunt[4] and found this to be satisfactory (Fig. 7).

The peroneal artery in our experience is difficult to expose deep in the leg beneath the soleus muscle. It is not uncommon for the artery to be enmeshed in a network of small veins. The peroneal was used 10 times in this series and we continue to use it if it appears to be the only adequate patent vessel by arteriogram.

In the patient with an adequate saphenous vein, various techniques have been described in efforts to restore flow. Dale,[1] in 1962, reported on a combination of Teflon and autogenous vein with a high early failure rate. More recently, Linton[7] and Lord[8] have reported a renewed interest in the use of the composite grafts of Dacron and autogenous vein to restore distal flow.

We have attempted to combine the use of an isolated popliteal segment and the patent distal vessels to achieve restoration of flow when a composite graft is necessary. Using the Dacron from the common femoral to the popliteal above the knee, we restore flow into this isolated segment and then carry the autogenous vein across the knee to the distal vessel. We prefer to place a vein patch onto the Dacron bypass, then to bring the vein bypass off this vein patch. This principle, first described by Linton,[7] has been used successfully in combined aorto-femoral disease.[5] Such a venous patch allows origin of the vein bypass to expand with inflow and not be stretched to the point of diminishing flow.

On several occasions, we have been faced with no autogenous tissue and no isolated popliteal segment above the knee. Rather than place a Dacron above the knee with no vessel to receive flow, we have resorted to homologous veins and the Sparks Mandril tube graft on two occasions. In one Sparks Mandril, we were able to restore flow into an anterior tibial and have it remain patent for 4 months. The second did not form an adequate collagen tube and could not be used. Both homologous veins functioned satisfactorily; one remains patent at 8 months while the second thrombosed at 4 months.

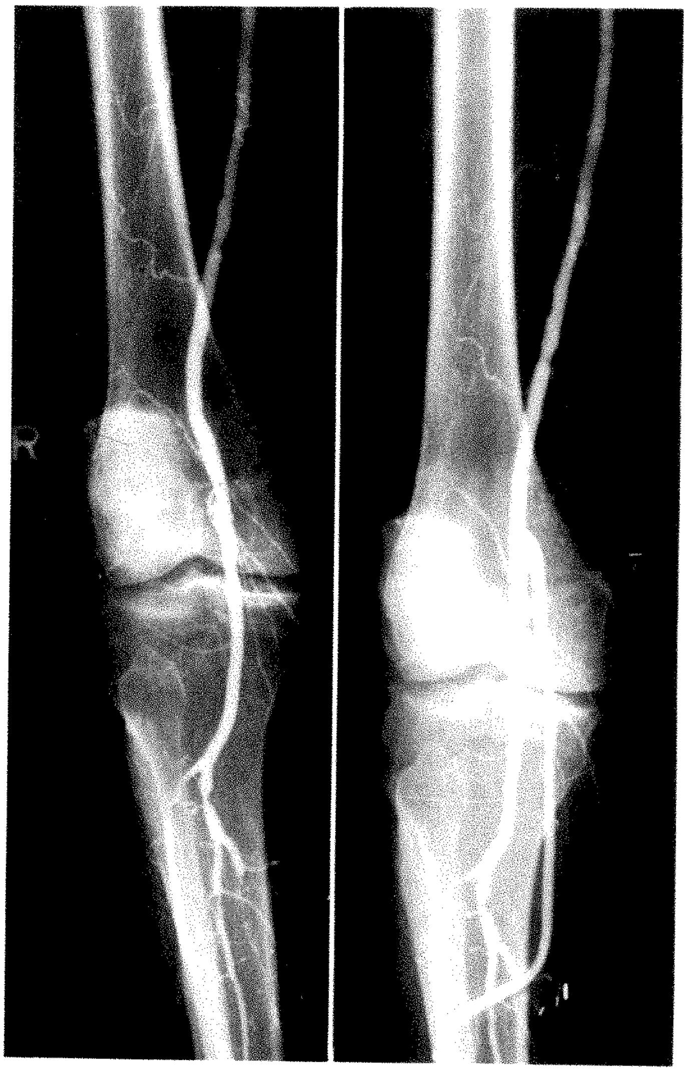


FIG. 7. The arteriogram of the left demonstrates stenosis of the proximal anterior tibial and common peroneal posterior tibial trunk with occlusion of the posterior tibial. The postoperative arteriogram on the right demonstrates the femoral to anterior tibial bypass tunnelled through the tibia.

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DISCUSSION

DR. EDWARD S. LINDSEY (New Orleans): Dr. Edwards, this very excellent paper certainly serves to remind us of the usefulness of perseverance. I assume, although you did not admit it, that you used magnifying loupes. In the last few years the use of this device has become central to the success of many of the small vessel anastomoses we do.

I feel intimidated, in a measure, by the cardiac surgeons who want to save every peripheral vein available to man. There is merit to this; we must be very prudent and avoid the abuse of veins which may be better employed in the future reconstruction of peripheral arteries.

I wonder if you have found bovine heterografts dependable? We have a large experience with bovine grafts in hemodialysis access operations, and have found them to be useful.

One other point I would appreciate your speaking to is the use, in some patients whose ischemia may be relatively acute, of fasciotomy; and by this I imply generous full-length fasciotomies, as others have spoken to.

And lastly, does sympathectomy have an application in any of these patients, particularly those with ulcers? In some patients in whom I am worried about the efficacy of sympathectomy, we have monitored changes of the calf and forefoot temperature with a thermocouple following spinal anesthesia; if temperature increases, we are more comfortable about proceeding with sympathectomy.

DR. WILLIAM H. EDWARDS (Closing discussion): I would like to thank Dr. Lindsey for his kind comments. I wear trifocals when I'm up here. I very definitely wear loupes when I'm operating on almost all arteries—not all, but almost all.

My early experience with bovine grafts was disastrous. I have not utilized these any more. As you well know, Dr. Dale has for some years used bovine, and on occasions, I think, probably still continues to use bovine grafts.

In the patient with acute ischemia we do at times use fasciotomy. I have not had enough experience to really know its place, but feel that, certainly, it has merit in times of swelling. This will sometimes save a distal bypass which otherwise might fail because of the compression.

I don't know the role of sympathectomy in peripheral occlusive disease. I do not use sympathectomy. I use general anesthesia for most of my patients and have never been able to determine exactly where sympathectomy should be used and where it should not be used, and I therefore do not utilize it extensively in this type of patient.

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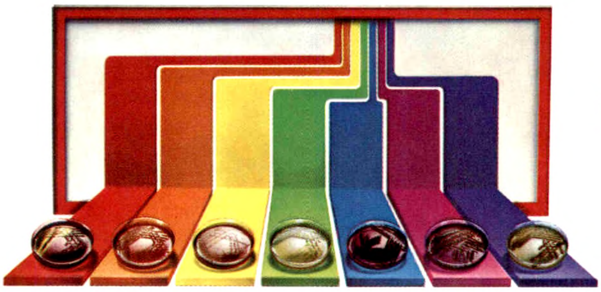
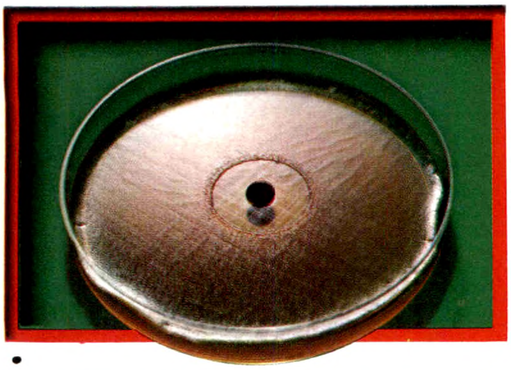
In serious gram-negative infections*

Three good reasons to initiate therapy with Garamycin® Injectable

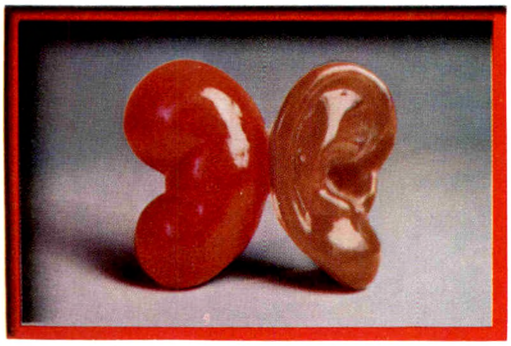
(gentamicin sulfate)



1. Unique spectrum.



2. Incidence of bacterial resistance is low and has not increased significantly.



3. Relatively low order of adverse renal and eighth nerve reactions when used as directed.

*Due to susceptible organisms

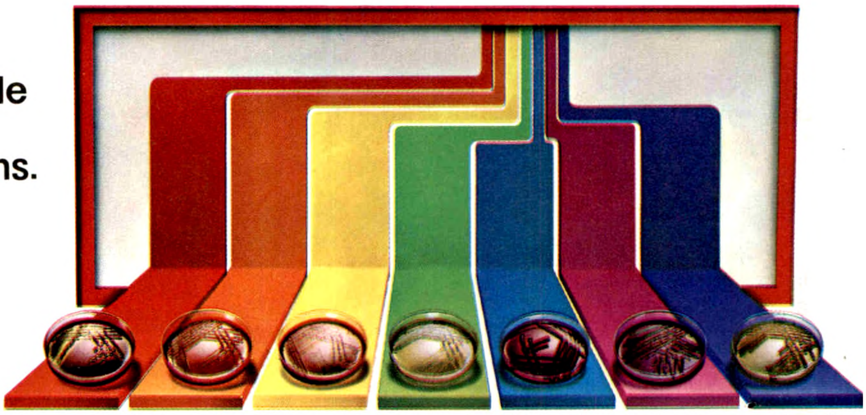
1. Unique spectrum.

Garamycin Injectable (gentamicin sulfate) is active against susceptible strains of seven major gram-negative pathogens.

These are:

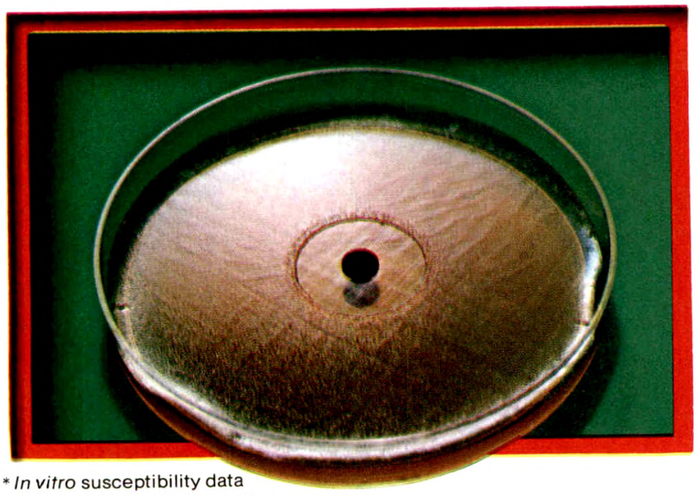
Escherichia coli
Proteus, indole-negative
Proteus, indole-positive
Pseudomonas aeruginosa
Klebsiella
Enterobacter } species
Serratia

Garamycin Injectable is also highly effective against susceptible strains of **Staphylococcus aureus** and may be considered when penicillins are contraindicated.



2. Incidence of bacterial resistance is low and has not increased significantly.

*In vitro** susceptibility virtually unchanged



* *In vitro* susceptibility data are not necessarily indicative of clinical effectiveness.

In a five-year study[1] in over 180 hospitals, gram-negative pathogens identified and tested demonstrated high susceptibility to GARAMYCIN. From 1971 through 1975 there was virtually no change in the percentage of strains of major gram-negative pathogens susceptible to GARAMYCIN.

In the seven or eight years' experience of one investigator[2] where gentamicin has been restricted to parenteral use, resistance has not appreciably changed.

Resistance has been demonstrated to develop slowly in stepwise fashion. No one-step mutations to high resistance have been reported.

References

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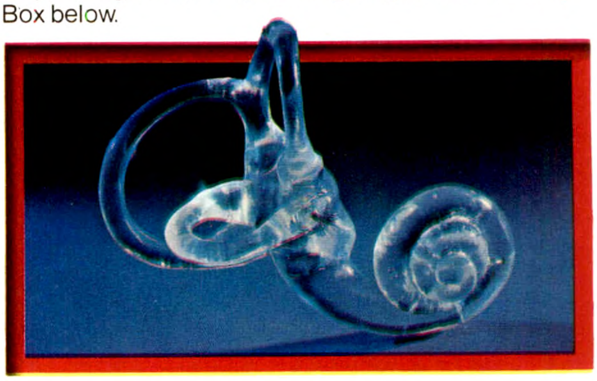
3. Relatively low order of adverse renal and eighth nerve reactions when used as directed.

Adverse renal reactions

The risk of adverse renal reactions is low in patients with normal renal function. Usually manifested by nitrogen retention as evidenced by a rising BUN and creatinine, they occur most often in patients with pre-existing renal damage and in patients receiving larger than recommended doses or treated for longer periods of time than recommended. See Warning Box below.

Adverse eighth nerve reactions

The incidence of adverse eighth nerve reactions with GARAMYCIN Injectable is relatively low. When occurring, the effect is predominantly on the vestibular branch of the eighth cranial nerve, resulting in vestibular dysfunction with vertigo and tinnitus. These symptoms have, in many cases, been transitory. The known effect on the auditory branch to date mostly has involved only the high-frequency hearing ranges. See Warning Box below.



A logical choice

in serious gram-negative infections†

pneumonia
urinary tract infections
septicemia
wound infections

† Due to susceptible organisms

Garamycin® I.M./I.V.
gentamicin sulfate 80mg/2ml.
injectable

40 mg./ml. Each ml. contains gentamicin sulfate equivalent to 40 mg. of gentamicin

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

See Clinical Considerations section which follows...

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A logical choice

in serious gram-negative infections*

GARAMYCIN® Injectable, brand of gentamicin sulfate, U.S.P., injection, 40 mg. per ml.
Each ml. contains gentamicin sulfate, U.S.P. equivalent to 40 mg. gentamicin.
For Parenteral Administration.

WARNING

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USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (indole-positive and indole-negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS:

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, agranulocytosis, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION
GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:
*Patients with normal renal function**

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lb.), the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

**In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.*

For Intravenous Administration:
The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused over a period of one to two hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., is supplied in 2 ml. (80 mg.) multiple-dose vials and in 1.5 ml. (60 mg.) and 2 ml. (80 mg.) disposable syringes for parenteral administration.

Also available, GARAMYCIN Pediatric Injectable, 10 mg. per ml., supplied in 2 ml. (20 mg.) multiple-dose vials for parenteral administration.

011 JUNE 1975
AHFS Category 8:12.28

For more complete prescribing details, consult Package Insert or Physicians' Desk Reference. Schering literature is also available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

Garamycin® I.M./I.V.
gentamicin sulfate 80mg/2ml.
injectable
40 mg./ml. Each ml. contains gentamicin sulfate equivalent to 40 mg. of gentamicin

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*Due to susceptible organisms

SLS-595

Pneumonectomy:

Review of 351 Cases

HARVEY HARMON, M.D., SCOTT FERGUS, M.D., FRANCIS H. COLE, M.D.

Among 351 patients undergoing pneumonectomy, the mortality was 6%, and when the operation was performed for malignant disease, the mortality was 8.5%. Much of the risk of the operation is associated with the age, physiologic state, and associated diseases which are prevalent in patients who require pneumonectomy. The conduct of the operative procedure itself is of paramount importance since complications clearly increase the mortality. Operative mishaps predispose to postoperative complications, and the addition of postoperative problems to the operative complications combine to bring the mortality to 24%. Careful hemostasis, meticulous technique, fluid and blood replacement, as well as careful preoperative and postoperative management combine to produce an acceptable mortality in this serious procedure.

From the Department of Surgery,
The University of Tennessee,
College of Medicine, Methodist Hospital,
West Tennessee Chest Disease Hospital,
Memphis, Tennessee

After the discovery of effective antibiotics, development of appropriate blood and fluid replacement therapy, and newer techniques of anesthesia, pneumonectomy has become a standard procedure, but even today the mortality risk is reported from 6 to 20% in recent surgical literature. In this paper experience with 351 patients having pneumonectomy over a 25-year period is reviewed. It was undertaken as an effort to determine what factors influenced the outcome of the procedure. The operations were performed in the Methodist Hospital and the West Tennessee Chest Disease Hospital in Memphis, Tennessee. The services are a part of the University of Tennessee Department of Surgery, and the management of all patients was performed in the customary relationship between residents and staff surgeons. Data were abstracted from the hospital records of these 351 patients and analyzed with the assistance of the data processing department of the Memphis and Shelby County Health Department.

The composition by age, sex, and race of the patient group is shown in Table 1, indicating the total number of deaths and mortality rates. Of 212 patients under 50 years of age, 7 died (3.3%), compared to 14 deaths in 139 patients over 50 years of age (10%). Not surprisingly, the data substantiated that the operation was more dangerous for males (8% mortality) than for females (2.6% mortality), and more for Negroes (8% mortality) than for Caucasians (5%).

The disease categories for which the operation was performed appear in Table 2. Pulmonary tuberculosis accounted for a majority of the operations (188) and carried a mortality rate of 5.3%. One hundred and seventeen operations for malignant neoplasm resulted in 10 deaths (8.5% mortality rate). Of 23 patients with bronchiectasis, none died. There was one death in the remaining 23 cases of fungus infection and other inflammatory disease. The total mortality rate for the 351 cases reported was 6%.

During the early years of this operative experience, inflammatory disease and tuberculosis were the most common indications for pneumonectomy. In more recent years, malignant disease has been the prime indication.

Presented at the Annual Meeting of the Southern Surgical Association, December 8–10, 1975, The Homestead, Hot Springs, Virginia.

TABLE 1. *Operative Mortality in Patient Groups*

Age	Total	Deaths (Rate)
20–49	212	7 (3.3%)
50–92	139	14 (10.0%)
Males	194	17 (8.0%)
Females	157	4 (2.6%)
Negro	145	11 (8.0%)
Caucasian	206	10 (5.0%)

Prior to 1959, of the 212 patients undergoing pneumonectomy, 10 died (4.7%). After 1959, of 139 operations performed, there were 11 deaths (8% mortality rate). Not all of these patients had formal pulmonary function studies, with many operations being performed simply after exercise tolerance tests and historical information of adequate pulmonary function. Of those tested, 82 had Maximum Voluntary Ventilation below 65% of predicted values, and 7 died (8.5%).

Associated diseases included diabetes, cardiovascular disease, arthritis and emphysema. Of 88 patients with these diseases, 11 died (12.5%), while only 10 deaths occurred in the remaining 263 patients who had no significant associated disease for a mortality rate of 3.8%.

It is generally known that right pneumonectomy is more dangerous than removal of the left lung. Detailed studies of the deaths indicate that the same causes are applicable on both sides, but occur more frequently in right sided operations. Certainly the removal of the right lung with its larger vascular bed imposes a greater physiologic burden than does left pneumonectomy. In our experience, of 224 left pulmonary resections, 8 died (3.5%), and of the 127 who had the right lung removed, 13 died (10%).

The right bronchial stump projects into the pleural space after pneumonectomy, while the left retracts into the shelter of the aortic arch. More tissue is available on the left for secondary suture over the stump to buttress the closure. Bronchopleural fistula occurred in 12% on the right side and only 6% of left pneumonectomies. The disastrous sequellae to bronchial leak account for part of the excess in deaths following right pneumonectomy.

A survey of these figures emphasizes the obvious fact that pneumonectomy is particularly dangerous in dyspneic men over 50 years of age with bronchogenic carcinoma, who have associated systemic disease and require operation on the right side, especially if they are black. Unfortunately, most of the people who need pneumonectomy have some or all of these characteristics.

TABLE 2. *Operative Mortality by Diagnosis*

	Total	Deaths (Rate)
Pulmonary Tuberculosis	188	10 (5.3%)
Carcinoma	117	10 (8.5%)
Bronchiectasis	23	0
Other	23	1 (4.0%)
Total	351	21 (6.0%)

Pulmonary tuberculosis and the other inflammatory diseases of the lung can now be so effectively managed by antibiotic therapy that they are essentially eliminated from the indications for operation, leaving malignant disease as the prime diagnosis in almost all patients who require pneumonectomy. The dreadful prognosis in lung cancer makes it extremely difficult to withhold surgical therapy from any patient in whom total removal of the disease process is feasible. It follows, therefore, that limitation of surgical treatment to good risk patients would be to abandon the only chance for cure in the majority of patients who have this fatal disease.

Measures to reduce bronchial secretions, optimal improvement of pulmonary function, control of infections and intensive treatment of associated disease are all worth a few days delay in an effort to improve the outcome of the operation. These factors are more directly under the control of the surgeon, along with careful anesthetic management and meticulous operative technique which will minimize operative complications (Table 3). Fifty-nine per cent of these patients (207 out of 351) survived the operative and postoperative period without complications and only 2 deaths occurred, representing a 1% mortality rate. Both these deaths resulted from pulmonary embolism. Operative complications occurred in a total of 79 patients, 45 (57%) of whom developed complications after surgery. In the remaining 34 patients, operative complications alone resulted in 2 deaths (6%). The 45 patients, who after an operative complication developed postoperative difficulties, had a death rate of 24%. The risk of postoperative complication in the remaining 65 patients without operative difficulties was 18% and in this group there were 6 deaths, representing a 9% mortality rate. Operative complications were defined as shock (blood pressure under 90 systolic for 20 minutes), hemorrhage (sudden rapid loss of over 300 cc of blood), cardiac arrhythmias, and operative injury. Preoperative irradiation, used at first by protocol and subsequently in a few specific clinical situations, predisposed to serious complications, and in 13 such patients 6 had opera-

TABLE 3. *Complications of Pneumonectomy*

	Number (Rate)	Deaths (Rate)
None	207 (59%)	2 (1.0%)
Operative only	34 (10%)	2 (6.0%)
Operative & postop	45 (13%)	11 (24.0%)
Postop only	65 (18%)	6 (9.0%)

TABLE 4. *Postoperative Complications*

Cardiac
Bronchopleural Fistula
Empyema without BPF
Shortness of Breath
Wound Infection or Disruption
Pulmonary Edema
Pericarditis
Hemorrhage
Miscellaneous

tive complications, 8 had postoperative complications, and 4 died. Bronchopleural fistula or empyema in the preoperative state of the patient necessitates extrapleural dissection and predisposes to a complicated and difficult postoperative course.

Postoperative complications are classified as indicated in Table 4. Cardiac arrhythmias occurred in 23 patients during the operation and in 45 additional patients during the postoperative period. All ages were affected, with arrhythmias occuring in 29 patients under the age of 50 and 39 in those over 50 years of age. Right pneumonectomy produced more arrhythmia than the left. None of these patients received prophylactic digitalis. The operative arrhythmias responded to ventilation, adjustment of anesthesia, and only occasionally was drug therapy necessary. Of the 45 arrhythmias occuring after surgery, spontaneous conversion occured in 22, while digitalis was used in 23. Postoperative cardiac arrhythmia contributed to death in 9 patients but was not the primary cause in any of the deaths.

The 21 surgical deaths are tabulated in Table 5. One patient died of ventricular fibrillation at the conclusion of a difficult extrapleural pneumonectomy, probably because of deficiency in blood replacement. The other technical death occurred in the recovery room when the ligatures slipped off the pulmonary artery. Two of the deaths due to embolism occurred many years ago when rapid transfusions were given by pumping air into the blood bottle. Massive air embolism was fatal in these two. Pulmonary embolism of more standard nature occurred in 5 patients, 7 to 60 days after pneumonectomy. In the latter case, the embolism occurred after routine thoracoplasty in a young woman with tuberculosis. Bronchopleural fistula occurred in 29 patients and was fatal in 5. Respiratory failure accounted for 4 deaths, metastatic malignant disease to the brain and to the adrenals occurred in one patient each, and one patient died quietly 8 hours after operation with pneumothorax collapsing his remaining lung.

TABLE 5. *Analysis of Deaths, Pneumonectomy*

Technical	2
Embolic	7
BPF	5
Respiratory Failure	4
Metastatic Disease	2
Pneumothorax	1

Six of these deaths occurred within 24 hours of the operation, 6 more within 30 days, while 9 survived up to 10 months, but each with a prolonged course dating back to a complication of the operation. It appears that 12 of the 21 deaths were from causes specific to pneumonectomy, while 9 resulted from disasters common to major surgery in the treatment of serious diseases.

DISCUSSION

DR. WARREN H. COLE (Asheville, North Carolina): I wondered if Dr. Harmon has seen a paper in the *British Medical Journal* about a month ago, written by a man named Amory, talking about the administration of Levamasol at the time of operation for carcinoma of the lung.

To me, those figures are just fantastic. They gave this drug at the time of the operation, and have had enough time now to observe two-year survivals, and the two-year survivals have been very highly significant—that is, the increase has been highly significant—in the patients who were under about 130 pounds, which means that they were underdosing their patients. They gave a certain dose to everybody, and the patients who were over 130 pounds did not get the significant increase in the two-year survivals.

But in a letter which he wrote me just a short time ago he said now they were giving a dose per kilo, which, of course, is what they should have done in the first place. All drugs of that sort should be given on the basis of per kilo. I asked him in a letter what his explanation was. He said: Either one of two things. Either this drug is stimulating our immune process, or it is killing off the cells circulating at the time of the operation.

And he showed something which I was sure of, that a major operation knocks down the immunologic response—or, rather, the immunologic reserve—of the patients. There isn't any doubt about that now. Ten years ago I wasn't so sure of it, but I'm positive now that a big operation will cut down the immunologic reserve.

We've got to find some way to protect the patient while he's down. This lasts all the way from five days to five weeks, and now we have a lowered immunologic reserve.

DR. JAMES R. JUDE (Miami, Florida): Pneumonectomies are becoming fairly rare, it seems, today, especially for carcinoma, where lobectomy, if anything, will be the best method of treatment, and especially, as Dr. Cole just mentioned, the possibilities of interrupting the immunological response.

I'd like to ask the authors if they would comment on the use of mediastinoscopy or a Chamberlain procedure to evaluate patients of carcinoma of the lung, since tuberculosis is practically nonexistent as far as carrying out pneumonectomies any longer today.

But whether or not they use these procedures, I know we do, and as a consequence, much more rarely do we have to carry out pneumonectomies.

DR. FREDERICK H. TAYLOR (Charlotte, North Carolina): There is one other complication that I'd like to mention, and that is herniation of the heart after partial resection of the pericardium. I have had two uch patients, both rather dramatic, because both went promptly our after closing their chest. I thought both had a blown pulmonary artery, so promptly reopened their chest, and found the pericardium had herniated into the site of surgery.

Both were salvaged, and I have since found out that these can be prevented by turning a flap of pleura, and repairing the pericardium.

Dr. Donald L. Paulson (Dallas, Texas): Many years ago, Dr. Shaw and I reviewed our results of pneumonectomy after five years. We found that one of three patients had some degree of respiratory insufficiency. These were patients in whom the pneumonectomies were done for carcinoma.

It's also true that the mortality of pneumonectomy for carcinoma is directly proportionate to the extent of the disease at the time of the resection. The more extensive the disease, the greater the mortality, and the greater the risk of morbidity.

It's for this reason that we have used mediastinoscopy and pulmonary arteriography in addition to the usual procedures of evaluation prior to considering a patient for pneumonectomy, and we feel we have lowered the risk of injudicious and unwise pneumonectomies by this procedure.

Dr. Francis H. Cole (Closing discussion): I'd like to thank all the discussers.

My senior relative, Dr. Warren Cole, continues to be ahead of most of us, and I really don't have any experience in the area of immediate chemotherapy. I think all of us tried various forms of paraoperative chemotherapy 15 and 20 years ago in a protocol, and most of the things that you did to patients were detrimental, and increased the morbidity and mortality, on the basis that the agents that we used at that time increased the immunologic deficit of the patient, right at the time when he needed all of his help in healing.

Dr. Jude and Dr. Paulson, I may say that we use pneumonectomy—correction, mediastinoscopy—almost routinely. Occasionally, with a palliative resection with hemoptysis or infection, in which you are going to plan to take out the lung for reasons other than hope of a cure—I think that's about the only instance in which we fail to try to totally stage our patients. And I thoroughly agree with you that this should be done. It not only reduces pneumonectomy, but it reduces also the ineffective thoracotomy, which is only harmful to a patient.

I must say that this is a rather peculiar subject, but we did want to just review the operation itself. Obviously, there is a salvage of a small percentage of patients in cancer surgery, and pneumonectomy particularly, and if the operation costs too much in the way of morbidity and mortality, then one must continue to evaluate his whole treatment program. Therefore, it's absolutely essential to keep the morbidity and mortality down in pneumonectomy.

Dr. Taylor, I saw one of those heart herniations when I was a resident, and I have never forgotten it, and I always do some kind of a patchwork on the pericardium, and we haven't had that problem in our recent experience.

BOOK REVIEWS

Operative Anatomy of the Abdomen and Pelvis: E. A. Edwards, P. D. Malone and J. D. McArthur, 418 pp. Philadelphia, Lea & Febiger, 1975.

This volume describes the pertinent anatomy and briefly the techniques of most abdominal operations, including urologic and gynecologic procedures. It is a pleasure to read; the printing is excellent, the writing clear and concise. Profusely illustrated, the drawings of Mr. Malone are uniformly outstanding. Over half the illustrations, however, are from other publications and the quality varies. Apparently, many of these have been reduced in size which resulted in very small type and indistinct guidelines in some.

In each chapter, the anatomical description is followed by a discussion of the related operations. The latter text is appropriate but in some areas, excessive consideration is given to operations rarely performed, and in at least one instance, the description is repetitive, i.e., celiac ganglionectomy. This reviewer found only one error: small bowel bypass operations for obesity are referred to as planned small bowel resections.

As stated in the preface, the book is intended for the surgeon early in his career and for this group, it can be recommended. The basic facts are provided and sufficient references for more detailed study are given.

Raymond Postlethwaite

Year Book of Cancer—1975: Clark and Cumley (Eds.), 655 pp. Chicago, Year Book Medical Publishers, 1975.

The 1975 year book of Cancer is published in the format standard for other monographs in the Year Book series. The 1975 edition is 100 pages longer than the 1974 edition (655 versus 549), and this is partly due to the inclusion into 1975 of a section evaluating the current literature in the field of radiation therapy. Generally, the book is divided into 32 sections, exclusive of the introduction, about half of which is devoted to neoplastic diseases affecting specific organ systems. The other half is related to topics such as pathology, roentgen diagnosis, nuclear medicine, radiotherapy, chemotherapy and hormone therapy, immunology and immunotherapy, anesthesiology, etc. There are even sections on reconstruction and rehabilitation, advanced tumors and terminal care, epidemiology, statistics and cancer control, genetics, biochemistry, and various phases of virology. The last section of the book deals with general animal tumors. Each section is composed of 8 to 15 abstracts of articles from the literature which are thought to represent the most significant contributions in the given area.

Most of the abstracts in the first half of the book are related to clinical medicine and thereby gleaned from journals representing the clinical literature. Almost without exception, the abstracts are concise and well-written. The figures and photographs are nicely reproduced and liberally used. After many of the abstracts, an editorial comment follows and then a general resume of the article stressing its significant points. Occasionally, additional references are mentioned in the editorial comments at the end of the abstract. Of further help is a section at the end of each chapter termed additional reading. Here is listed a bibliography of other articles published in the relevant area during the preceding year. Frequently, an editorial comment follows the bibliographic reference identified to help the reader in evaluating the article.

By necessity, the selection is limited and any investigator, in either clinical or basic science, might argue with some of the articles included or others deleted. Nevertheless, the editorial board has done an admirable job in compiling the text in an organized and readable fashion. Topics such as biochemistry, radiobiology, and radiophysics, biology, molecular biology and virology may at firsthand seem infrequent reading topics for most clinicians. However, they are integral parts of oncology and the abstracts are presented in such a way that one can gain an overview of these areas most efficiently.

The Year Book series is in its 75th year, and continues to serve a useful function to scientists in many disciplines. This Year Book is well done, and provides a continuum in the yearly review of the oncological literature.

Dr. Samuel A. Wells, Jr.

Coronary Artery Medicine and Surgery: Concepts and Controversies: John C. Norman, Ed., 1073 pp. $68.50; New York, Appleton-Century-Crofts, 1975.

This text is the bound compilation of a symposium on "Coronary Artery Medicine and Surgery" held at the Texas Heart Institute in February of 1975.

Attractively printed, with clear text and excellent line and photographic copy, there are only minor proofing errors.

Dr. Theodore Cooper's superb introduction is followed by an excellent overview of operative and medicinal treatment for coronary artery disease. Other highlights include a good selection of papers discussing coronary pressure-flow relationships as they relate to revascularization procedures and some provocative essays on myocardial protection, variant angina and long term studies of the pathology of aorto-coronary saphenous vein bypass grafts.

The summated bibliographies from the 124 papers provided a comprehensive set of references for interested readers, but the repetition without cross indexing seems wasteful. The major weakness of the text is the consequence of its structural intent. Despite groupings of apparently related papers, the flow of content is disjointed, there is no editorial presence felt and there is no lack of discrimination between fine statistical presentations and anecdotal accounts. Inclusion of discussion among participants might have helped bridge some of the gaps and provided more of the unification that is missing. Unfortunately, the "concepts and controversy" are lost in a parade of "materials and methods." Since the papers published were initially offered for presentation rather than solicited, certain areas suffer the absence of contributions from centers with specific major expertise and experience.

Dr. Norman deserves commendation for his recognition of the need to provide to the medical profession information accrued at such symposia. Despite laudable efforts to provide timely publication, most of the series reported terminate in 1973 rendering the text less current than most contemporary journals in the field covering the same subject material.

At a much lesser price and published in less formal manner the proceedings of the meeting would be of interest.

Atlas of Applied Vascular Surgery: Kiyoshi Inokuchi and Akira Kusaba, 198 pp. Philadelphia, J. B. Lippincott Co., 1975.

RATHER THAN AN ATLAS of vascular surgery, this is an extensive monograph describing the end-to-end vascular stapling device of Dr. Inokuchi and its application as practiced by the authors at Kyushu University. The descriptions of the instrument are thorough and reveal a mechanical complexity that requires a novice to perform experimental trials before attempting its clinical use. Such background animal work as done by the authors is presented to demonstrate the superior results of this instrument over standard manual suturing techniques.

This instrument has permitted the authors to treat a variety of diseases with unusual vascular manipulations. Their book thus forms a compendium of unorthodox procedures, many of which have yet to prove to be lasting contributions to surgical therapy. The small vessel anastomoses as allowed by this technique enlarge the possibilities of autologous organ transplantation and permit unusual vascular shunts to provide metabolic and mechanical alterations of disease states. Although the value of many of the procedures remains to be established, the ingenuity of their concepts is impressive.

Unfortunately this book suffers from a language obstacle. Clumsy syntax, errors in grammar, and misspellings detract from the experience of examining the novel concepts these authors present. This is a serious defect in such a work where communication of new ideas is stressed more than the technical descriptions of operative procedures.

DR. JAMES C. A. FUCHS

Physiological Basis of Anaesthesiology: Mushin et al., $20.00; 367 pp. Padua, Italy, Piccin Medical Books, 1975.

THIS VOLUME is a collection of papers, cast largely in the format of reviews, presented at the First International Seminar on the Physiological Basis of Anesthesiology held in Milan in 1973. The subject, as it directly relates to anesthesia, is somewhat limited and, because of this, the book will have little appeal to the practicing anesthesiologist. However, those chapters dealing with the principles of automatic ventilation by Mushin, the uptake of volatile anesthetics by Salanitre, and the intriguing presentation by John Severinghaus of harmful drug interactions in respiratory control, are of considerable interest. For the most part, the material deals with the respiratory system, with outstanding presentations by Mead on mechanics; on distribution of ventilation by Milic-Emili; and ventilation perfusion by John West. Other presentations by Scarpelli and Macklem, as they relate to pulmonary surfactant, gas diffusion, respiratory reflexes, and automatic control of airway caliber, are clearly and effectively presented. The materials dealing with circulatory physiology, particularly an analysis of shock, are less rewarding. The value, however, of the volume lies in the excellence of the reviews, the extensive recent bibliography, the frequent use of graphs and figures. This book will be of major interest to those interested in respiratory physiology and its applications.

DR. ENRICO CAMPORESI
DR. MEREL HARMEL

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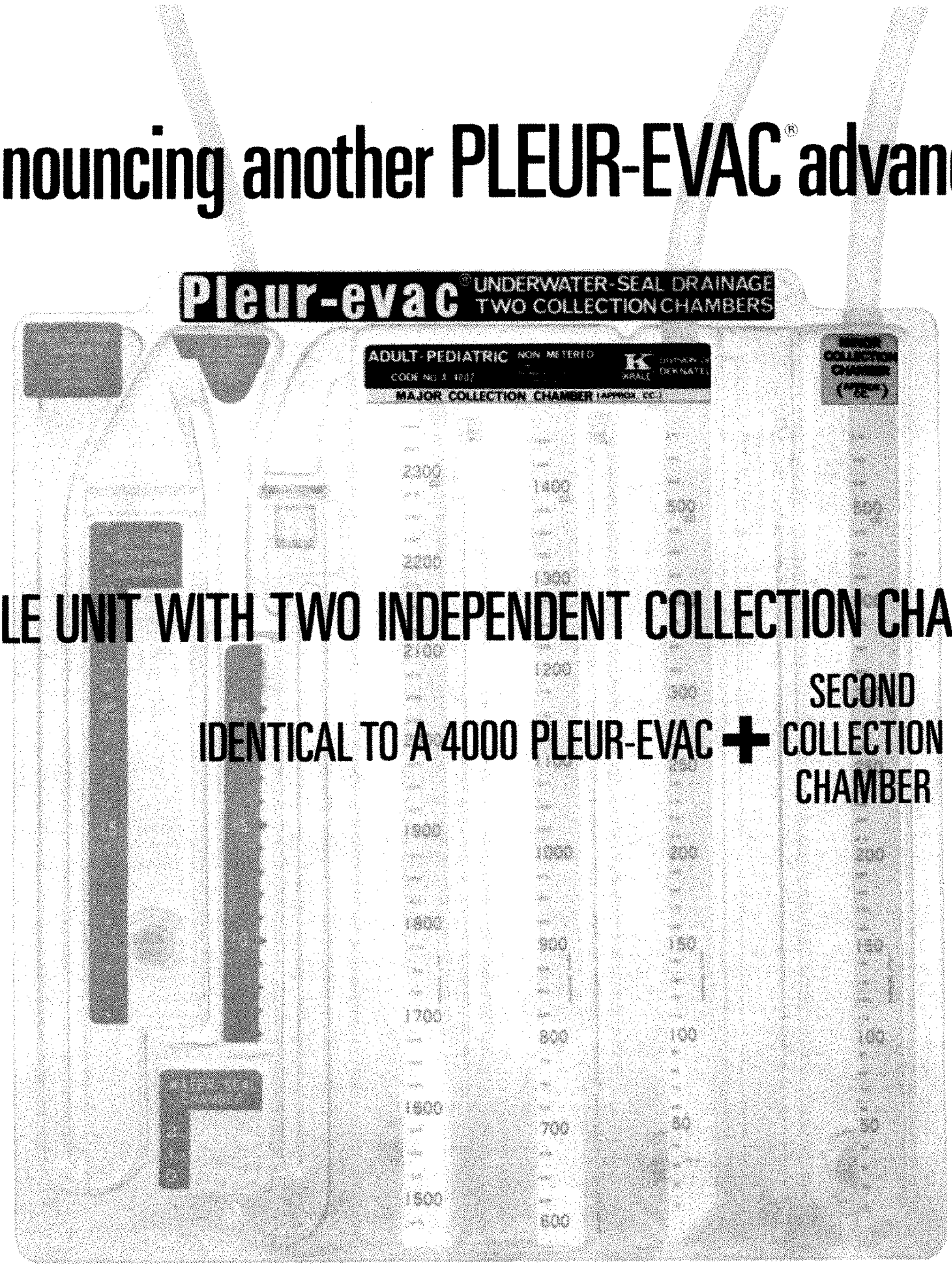
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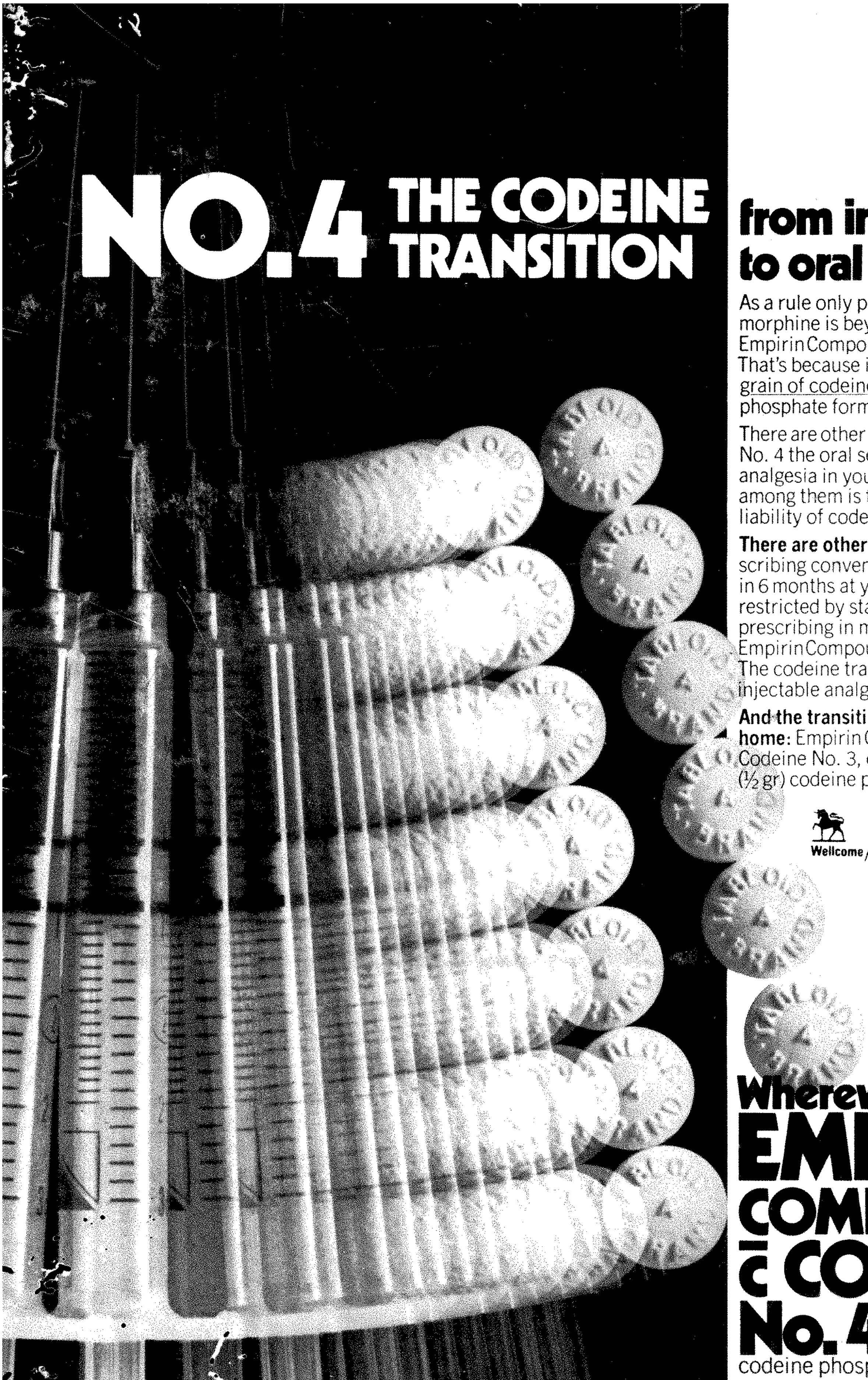

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